EXAMPLE 33

Topical KGF-2 in Infected Incisional Wounds

[1050] Bacterial infection of wounds continues to be of great clinical importance. Under normal situations, the complex process of wound healing progresses without difficulty. However, inoculation of a wound by bacteria causes an imbalance of cellular mediators in the inflammatory response resulting in delayed wound healing. Contamination of the open wound inhibits the wound healing process as characterized by decreased wound contraction, lower than normal wound collagen content and decreased tensile strength. Male adult Sprague Dawley rats (n+10/group) were anesthetized with a combination of ketamine (53 mg/kg im) and xylazine (5.3 mg/kg im) on day 1. The dorsal region was shaved and disinfected with 70% alcohol. A full thickness (through the epidermis, dermis to the subcutaneous layer) 2.5 cm surgical wound was created starting approximately 1 cm below the shoulder blades using a sterile no. 10 scalpel. Wounds were coated with 3 equidistant skin staples. The incisions were then inoculated intraincisionally with Staphylococcus aureus (107 cfu/ 50 μl) in PBS. KGF-2 Δ33 was applied topically at the time of wounding (Day 0) at doses of 0.1, 1 and 10 μg per wound in a volume of 50 μl. Wounds were then covered with a gas permeable occlusive dressing (Tegaderm). Animals were sacrificed on day 5 by anesthesia with ketamine/xylazine followed by lethal intracardiac administration of sodium pentobarbital (300 mg/kg). The middle 0.5 cm segment of the wound was excised and snap frozen for collagen determination. Two additional wound strips measuring 0.5 cm in width were excised. Excised wound strips were used for the study of breaking strength using an Instron skin tensiometer. Breaking strength was defined as the greatest force withheld by each wound prior to rupture using and 11 1b load cell at a speed of 0 mm/sec. Two values for each animal were averaged to provide a mean breaking strength value per wound. Statistical analysis was done using an unpaired t test (mean $\pm$ SE).

[1051] Intraincisional application of Staphylococcus aureus in the wound resulted in a significant impairment in wound healing as measured by breaking strength (noninfected wound treated with bacteria vehicle 136 ± 6g; infected wound 87 ± 6 g; p<0.0001 in one experiment; noninfected wound treated with bacteria vehicle 200 ± 14g; infected wound 154±10 g p=0.01 in another experiment). Topical administration of KGF-2 caused an increase in breaking strength which was statistically significant at the 0.1, 1 and 10 μg doses when compared with the KGF-2 buffer + S. aureus control (KGF-2 0.1 μg 152 ± 16 g (p=0.002); 1 μg 135± 12 g (p=0.003); 10 μg 158 ± 10g (p<0.0001) in one experiment; 0.1 μg 185±10g (p=0.03); 1 μg 186±11g (p=0.03); 10 μg 190±7g p+0.009) in another experiment). Collagen analysis of the middle 0.5 cm wound strip revealed that there was increased collagen content in KGF-2 treated wounds. However, when compared with the buffer controls, a statistically significant increase in collagen content was not observed.

[1052] The studies described in this example test activity in KGF-2 Δ33 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ28, and polypeptide comprising encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 33

Proliferative effect of dosing i.v. every other day with 1 mg/kg of KGF-2Δ33

[1053] Male Sprague Dawley rats were intravenously injected with either KGF-2 Δ33 at a dose of 1 mg/kg, or buffer. The animals were injected either daily or every other day. Each treatment group was injected for one week and sacrificed at the end of the week. On the day of sacrifice, the animals were injected i.p. with 100 mg/kg of BrdU. Two hours later, the animals were sacrificed, and the

serum was collected. Various tissues were collected and fixed in 10% neutral buffered formalin. The tissues were processed for histological evaluation. The tissues were stained with hematocylin and eosin, periodic-acid-Schiff, or alcian blue. Additional sections were subjected to immunohistochemical staining with an anti-BrdU antibody. Proliferation was quantitated using an image analysis spectrum, IPlab Spectrum. The serum chemistry analysis was performed using an automated chemistry analyzer. The following parameters were quantitated: thyroid gland weight; proliferation of goblet cells in the small intestine (duodenum, jejunum and ileum); proliferation of goblet cells in the colon; proliferation in the parotid and submandibular glands; and serum chemistry analytes (glucose, BUN, calcium, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol, and triglycerides).

[1054] In the small intestine and colon, daily treatment with KGF-2 caused a significant increase in the number of goblet cells. The every other day treatment did cause a slight increase in the number of goblet cells, however, it did not attain a statistically significant level. In the salivary gland, an increase in cells was observed in the parotid gland only. There was no difference between the treatment groups. There was an enlargement of the thyroid gland due to both dosing regimens. The magnitude of this increase was greater in the daily treatment group. Daily treatment with KGF-2 resulted in statistically significant increase in the following analytes: triglycerides, alkaline phosphatase, calcium, albumin, and total protein. The every other day treatment had no effect on these analytes. Cholesterol levels were elevated in both treatment groups. However, the magnitude of the increase was greater in the daily treatment group. Markers of cellular injury, such as ALT and AST, were similarly reduced in both treatment groups.

[1055] The studies described in this example test activity in KGF-2 Δ33 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ28, and polypeptide comprising encoding amino acids

77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 34

Formulating a Polypeptide

[1056] The KGF-2 composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the KGF-2 polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[1057] As a general proposition, the total pharmaceutically effective amount of KGF-2 administered parenterally per dose will be in the range of about 1μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, KGF-2 is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[1058] Pharmaceutical compositions containing KGF-2 are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of

administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[1059] KGF-2 is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped KGF-2 polypeptides. Liposomes containing the KGF-2 are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

[1060] For parenteral administration, in one embodiment, KGF-2 is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

[1061] Generally, the formulations are prepared by contacting KGF-2 uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the

blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[1062] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[1063] KGF-2 is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[1064] KGF-2 used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[1065] KGF-2 polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous KGF-2 polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized KGF-2 polypeptide using bacteriostatic Water-for-Injection.

[1066] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, KGF-2 may be employed in conjunction with other therapeutic compounds.

[1067] The compositions of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the compositions of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1068] In one embodiment, the compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899),, endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No.

WO 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[1069] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[1070] In a further embodiment, the compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the compositions of the invention include, but are not limited to, tetracycline, metronidazole, amoxicillin, beta-lactamases, aminoglycosides, macrolides, quinolones, fluoroquinolones, cephalosporins, erythromycin, ciprofloxacin, and streptomycin.

[1071] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome,

difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap. Also included are corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin), as well as antihistamines,

[1072] In another embodiment, compostions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[1073] In an additional embodiment, the compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the compositions of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha.

[1074] In an additional embodiment, the compositions of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Gorwth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

[1075] In an additional embodiment, the compositions of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[1076] In additional embodiments, the compositions of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

EXAMPLE 35

Method of Treating Decreased Levels of KGF-2

[1077] The present invention also relates to a method for treating an individual in need of an increased level of KGF-2 activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of KGF-2 or an agonist thereof.

[1078] Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of KGF-2 in an individual can be treated by administering KGF-2, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of KGF-2 polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of KGF-2 to increase the activity level of KGF-2 in such an individual.

[1079] For example, a patient with decreased levels of KGF-2 polypeptide receives a daily dose 0.1-100 μg/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 24.

EXAMPLE 36

Method of Treating Increased Levels of KGF-2

[1080] The present invention relates to a method for treating an individual in need of a decreased level of KGF-2 activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of KGF-2 antagonist. Preferred antagonists for use in the present invention are KGF-2-specific antibodies.

[1081] Antisense technology is used to inhibit production of KGF-2. This technology is one example of a method of decreasing levels of KGF-2 polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

[1082] For example, a patient diagnosed with abnormally increased levels of KGF-2 is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 24.

EXAMPLE 37

Method of Treatment Using Gene Therapy - Ex Vivo

[1083] One method of gene therapy transplants fibroblasts, which are capable of expressing KGF-2 polypeptides, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

[1084] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[1085] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with

EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1086] The cDNA encoding KGF-2 can be amplified using PCR primers which correspond to the 5′ and 3′ end sequences respectively as set forth in Example 1. Preferably, the 5′ primer contains an EcoRI site and the 3′ primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector contains properly inserted KGF-2.

[1087] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the KGF-2 gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the KGF-2 gene(the packaging cells are now referred to as producer cells).

[1088] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether KGF-2 protein is produced.

[1089] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

EXAMPLE 38

Gene Therapy Using Endogenous KGF-2 Gene

[1090] Another method of gene therapy according to the present invention involves operably associating the endogenous KGF-2 sequence with a promoter via homologous recombination as described, for example, in U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller *et al., Proc. Natl. Acad. Sci. USA 86*:8932-8935 (1989); and Zijlstra *et al., Nature 342*:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

[1091] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5′ non-coding sequence of endogenous KGF-2, flanking the promoter. The targeting sequence will be sufficiently near the 5′ end of KGF-2 so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5′ and 3′ ends. Preferably, the 3′ end of the first targeting sequence contains the same restriction enzyme site as the 5′ end of the amplified promoter and the 5′ end of the second targeting sequence contains the same restriction site as the 3′ end of the amplified promoter.The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting

mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

[1092] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[1093] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous KGF-2 sequence. This results in the expression of KGF-2 in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[1094] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

[1095] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the KGF-2 locus, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5′ end and a BamHI site on the 3′end. Two KGF-2 non-coding sequences are amplified via PCR: one KGF-2 non-coding sequence (KGF-2 fragment 1) is amplified with a HindIII site at the 5′ end and an Xba site at the 3′end; the other KGF-2 non-coding sequence (KGF-2

fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and KGF-2 fragments are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; KGF-2 fragment 1 - XbaI; KGF-2 fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[1096] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately 1.5.X10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[1097] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37°C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[1098] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

EXAMPLE 39

Method of Treatment Using Gene Therapy - In Vivo

[1099] Advances in gene research have resulted in the development of techniques to deliver and express genes in human cells. The ideal goal for gene therapy is the delivery of normal genes in order to generate active proteins and compensate for the lack of endogenous production (Gorecki, D.C. *et al.*, *Arch. Immunol. Ther. Exp. 45(5-6)*:375-381 (1997)).

[1100] Delivery of genes encoding cytokines or growth factors involved in the different phases of wound healing and tissue repair have the potential to modify the outcome of wound healing (Taub, P.J. *et al.*, *J. Reconst. Microsur. 14(6)*:387-390 (1998)). The use of cDNA of growth factors or other cytokines for wound healing and tissue repair has been extensively described (Tchorzewski, M.T. *et al.*, *J. Surg. Res. 77*:99-103(1998)). Genes transferred by a vector can be used to generate new cell lines, identify transplanted cells and express growth factors or enzymes. One of the advantages of gene therapy is to achieve therapeutic concentrations of gene-derived protein locally within the lesion site. Human recombinant KGF-2 protein has been shown to stimulate wound healing of the skin, gastro-intestinal tract and other organ containing cells of epithelial origin. The use of KGF-2 gene is expected to have similar pharmacological profile as the recombinant protein. KGF-2 gene may be involved in events related to tissue repair such as cell proliferation, migration and the formation of extracellular matrix.

[1101] Transcribed and translated cDNA has been used to deliver genes to sites of interest. Some examples of genes used in this fashion include aFGF, BMP-7 (Breitbart, A.S. *et al.*, *Ann. Plast. Surg. 24(5)*:488-495 (1999)). These cells have also been seeded into cell carriers including biodegradable matrices (ex. polyglycoloic acid), tissue substitutes or equivalents (ex. artificial skin), artificial organs, collagen-derived matrices, etc. Liposomes have been used to carry

cDNA. PDGF-BB cDNA in haemagglutinating virus of Japan (HVJ)-liposome suspension was studied in the healing of patellar ligament (Nakamura *et al.*, *Gene Ther. 5(9)*:1165-1170 (1998)). Genes can also be delivered directly to the site of action by direct injection (ex. heart).

[1102] Thus, another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) KGF-2 sequences into an animal to increase or decrease the expression of the KGF-2 polypeptide. The KGF-2 polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the KGF-2 polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata, H., *et al.*, *Cardiovasc. Res. 35*(3):470-479 (1997), Chao, J., *et al.*, *Pharmacol. Res. 35*(6):517-522 (1997), Wolff, J.A., *Neuromuscul. Disord. 7*(5):314-318 (1997), Schwartz B., et al., *Gene Ther. 3*(5):405-411 (1996), Tsurumi, Y., *et al.*, *Circulation 94*(12):3281-3290 (1996) (incorporated herein by reference).

[1103] The KGF-2 polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The KGF-2 polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1104] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the KGF-2 polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. *et al.*, *Ann. NY Acad. Sci. 772*:126-139 (1995) and

Abdallah B. *et al., Biol. Cell 85*(1):1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

[1105] The KGF-2 polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[1106] The KGF-2 polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *in vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[1107] For the naked KGF-2 polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked KGF-2 polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1108] The dose response effects of injected KGF-2 polynucleotide in muscle *in vivo* is determined as follows. Suitable KGF-2 template DNA for production of mRNA coding for KGF-2 polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1109] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The KGF-2 template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[1110] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for KGF-2 protein expression. A time course for KGF-2 protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of KGF-2 DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using KGF-2 naked DNA.

EXAMPLE 40

KGF-2 Therapy for Inflammatory Bowel Disease

[1111] In this example, the inhibition of pathologic changes in colons of mice caused by exposure to dextran sodium sulfate (DSS) in drinking water by systemic (intranasal) and intraperotineal administration of KGF-2 polynucleotides is determined.

[1112] Intranasal administration. A polynucleotide encoding KGF-2 Δ33 is introduced into the nasal passages of anaesthetized female Swiss Webster mice (n=10/group) through a blunted 26 gauge needle at a dosage of 1, 10 or 100 μg of polynucleotide. Control polynucleotide is administered to a separate group of mice. Five days after intranasal administration of the polynucleotide, 5% DSS is added to the drinking water. Mice are monitored for body weight, hematocrit, and stool score. After seven days of exposure to DSS in the drinking water, mice are sacrificed. Histopathologic assessment of colon and small intestine is performed. RT-PCR analysis is performed to determine expression of KGF-2 in liver, spleen and colon.

[1113] Intraperotineal administration. A polynucleotide encoding KGF-2 Δ33 is injected intraperitoneally into female Swiss Webster mice (n=10/group) through a blunted 26 gauge needle at a dosage of 1, 10 or 100 μg of polynucleotide on days 0 and 3. Control polynucleotide is administered to a separate group of mice using and identical regimen. On day 7, 5% DSS is added to the drinking water. Mice are monitored for body weight, hematocrit, and stool score. On day 14, mice are sacrificed. Histopathologic assessment of colon and small intestine is performed. RT-PCR analysis is performed to determine expression of KGF-2 in liver, diaphragm and colon.

[1114] The studies described in this example test activity in KGF-2 Δ33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; and any KGF-2 mutant described herein.

EXAMPLE 41

KGF-2 Therapy for Ocular Surface Disease

[1115] In this example, the effect of subconjuctival administration of Δ33 KGF-2 polynucleotides on the conjunctiva, cornea or lacrimal gland of rats is determined.

[1116] A polynucleotide encoding Δ33 KGF-2 is injected into the subconjuctival space of anaesthetized Female Sprague Dawley rats (150-200 g body weight, 6/treatment group) at a dosage of 1, 10 or 100 μg. Control polynucleotide is injected in a similar fashion to a separate group of control rats. Separate groups of rats are sacrificed at 3, 7 and 14 days post injection. BrdU is administered intraperitoneally to some of the rats 30 minutes before euthanasia.

The eye and surrounding tissues are removed for histologic analysis. The extent of BrdU incorporation in the epithelial cells of the cornea, conjunctiva and lacrimal glands is measured. The thickness of the epithelial layer in the cornea and conjunctiva is assessed. The number of goblet cells in the conjunctiva is measured.

[1117] The studies described in this example test activity in KGF-2 Δ33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 42

KGF-2 Therapy for Salivary Gland Dysfunction

[1118] In this example, the effect of KGF-2 polynucleotide administration into the papillae of the parotid salivary gland duct of normal rats on the epithelial cells of the ducts and acini of that gland is determined.

[1119] Female Sprague Dawley Rats (150-250 grams, 6/group) are anesthetized by the intramuscular injection of ketamine and xylazine. A polynucleotide encoding Δ33 KGF-2 is introduced into the papilla of the parotid salivary gland using a 30 gauge steel gavage needle, at a dosage of 1, 10 or 100 μg. The polynucleotide is infused over a ten minute period at a rate of 1 μl per minute. Control polynucleotide is administered to a separate group of rats. Separate groups of rats are sacrificed at 3, 7 and 14 days after infusion. BrdU is administered intraperitoneally 30 minutes before euthanasia. The salivary glands are weighed, and the number of BrdU-staining cells is counted on histologic

section. In a separate experiment, pilocarpine-stimulated saliva secretion is measured in rats at 7 days after infusion.

[1120] The studies described in this example test activity in KGF-2 Δ33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 43

KGF-2 Therapy for Dermal Wound Healing

[1121] In this example, the ability of KGF-2 polynucleotide to stimulate wound healing in the normal rat and diabetic mice is determined.

[1122] Normal rat. Anesthetized female Sprague Dawley rats (175-250 gm 6/treatment group) are wounded with 8 mm biopsy punches. Δ33 KGF-2 polynucleotide (1, 10 or 30 μg) is delivered intradermally at 4 different sites along the wound. Control polynucleotide is administered in a similar manner to a separate group of rats. The wounds are covered with sterile ventilated fabric pads. After the pad is positioned, waterproof adhesive tape is wrapped around the midsection of the rat. Separate groups of rats are sacrificed at 2 and 5 days post wounding. The wound tissues are fixed in 10% formalin embedded in paraffin. BrdU incorporation in proliferating epithelial cells in pre-existing and new epidermis, and the length and thickness of the new epithelial tongue is measured.

[1123] Diabetic mice. Diabetic mice (db+/db+, 10/treatment group) and nondiabetic mice (db+/m+, 10/treatment group) are wounded with a 6 mm punch wound in the dorsum. Δ33 KGF-2 polynucleotide (1, 10 or 30 μg) is delivered intradermally at 4 different sites along the wound. Control polynucleotide is

administered in a similar manner to a separate group of mice. The wounds are covered with Tegaderm (diabetic mice) or Tegaderm plus adhesive tape (nondiabetic mice). The wounds are photographed on days 0, 3, 7, 10 and 14 post wounding. The surface area of the wounds are measured by image analysis.

[1124] The studies described in this example test activity in KGF-2 Δ33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 44

Constructs for KGF-2 delivery

[1125] An appropriate construct for KGF-2 gene therapy delivery is pVGI.0-KGF-2. This construct contains the full native open reading frame of KGF-2 cloned into the expression vector pVGI.0. pVGI.0 contains a kanamycin resistance gene, a CMV enhancer, and an RSV promoter. pVGI.0-KGF-2 was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, on June 30, 1999, and given ATCC Deposit No. PTA290. This construct was made by subcloning the KGF-2 ORF from a previously sequence verified KGF-2 construct into the expression vector pVGI-0, using methods well known in the art.

[1126] Another appropriate construct for KGF-2 delivery is pVGI-0-MPIFspKGF2Δ33. This construct contains the native sequence of KGF-2 Δ 33 fused to the MPIF (CKβ 8) heterologous signal peptide cloned into the expression vector pVGI-0. pVGI.0-MPIFspKGF2Δ33 was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas,

VA 20110-2209, on June 30, 1999, and given ATCC Deposit No. PTA289. This construct was made using methods well known in the art and the following primers:

5' primer:

GAGCGCGGATCCGCCACCATGAAGGTCTCCGTGGCTGCCCTCTCC TGCCTCATGCTTGTTACTGCCCTTGGATCTCAGGCCAGCTACAATCA CCTTCAAGGAGATG (SEQ ID NO:149)

3' primer: GAGCGC GGATCC CTATGAGTGTACCACCATTGGAAG (SEQ ID NO:150)

EXAMPLE 45

Angiogenesis During KGF-2 Gene Therapy

[1127] Characterization of the multiple aspects of microvascular physiology in transparent window systems in mice have provided valuable data on angiogenesis, inflammation, microvascular transport, tissue rejection and tumor physiology. In this example, the development of vasculature during a wound healing response in implanted collagen gels is assessed through direct observation of the tissue and associated microvascular bed through an implanted skin window. This model is used to determine if KGF-2 gene therapy can simultaneously induce an accelerated tissue regrowth and revascularization.

[1128] Skin biopsies from nude mice are digested in collagenase, the resulting cell suspensions washed and then cultured in DMEM with 10% FBS to obtain dermal fibroblasts. Confluent fibroblast cultures are transfected with KGF-2 or control polynucleotide then collected and washed in PBS. 106 cells are suspended in 20 μl of collagen matrix. Samples of cell suspension are removed for Western blot confirmation of KGF-2 production. A 2 mm punch biopsy is made into an existing dorsal skin window and the skin sandwiched between two glass coverslips. The cell collagen mixture is placed into the circular wound and

the chamber sealed. The implanted gels are observed at regular intervals for vessel development. Tissue regrowth into the wound is monitored as changes in the optical density of the collagen gel over a three week period. Tissue from the dorsal chambers is removed following the conclusion of the study for histological evaluation. Control experiments involve the addition of KGF-2 polypeptide or buffer into collagen gels in place of fibroblasts.

[1129] Mouse preparation. The surgical procedures are performed in Swiss nude mice. For the surgical procedures, animals (20-30 g) are anesthetized with s.c. injection of a cocktail of 90 mg Ketamine and 9 mg Xylazine per kg body weight. All surgical procedures are performed under aseptic conditions in a horizontal laminar flow hood, with all equipment being steam, gas or chemically sterilized. During surgery, the body temperature of the animals is kept constant by means of a heated work surface. All mice are housed individually in miscroisolator cages and all manipulations are done in laminar flow hoods. Buprenorphine (0.1 mg/kg q 12h) is administered as an analgesic for 3 days post implantation.

[1130] Mice are positioned such that the chamber is sandwiched between a double layer of skin that extends above the dorsal surface. One layer of skin is removed in a circular area ~15 mm in diameter. The second layer (consisting of epidermis, fascia, and striated muscle) is positioned on the frame of the chamber and covered with a sterile glass coverslip. The chamber is held in place with nylon posts which pass through the extended skin and holes along the top of the chamber. After 3 days, the coverslip is carefully removed and the gel inserted. A new, sterile coverslip is then placed on the viewing surface. Measurements are made by morphometric analysis using an Intensified CCD camera, S-VHS videocassette recorder and direct digital image acquisition. Mice with implanted changers were observed for 28 days.

[1131] Measurements. Mice are anesthetized with s.c. injection of a cocktail of 90 mg Ketamine and 9 mg Xylazine per kg body weight, then positioned on a sterile plastic stage assembly. Vascular maps of the window are made using transillumination (dorsal skin window) or following an injection of 100 μl of

BSA-FITC (1 mg/ml, i.v.) and epi-illumination. Video recordings of vascular beds are made at a range of magnifications (from 1X to 40X) as well as digital frames for off-line analysis. Angiogenesis determinations of implanted gels are made from offline analysis of video tapes.

[1132] The studies described in this example test activity in KGF-2 Δ33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any of the KGF-2 mutants described herein.

EXAMPLE 46

KGF-2 Transgenic Animals

[1133] The KGF-2 polypeptides can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

[1134] Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver *et al., Biotechnology (NY) 11*:1263-1270 (1993); Wright *et al., Biotechnology (NY) 9*:830-834 (1991); and Hoppe *et al.*, U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten *et al.*,

Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson *et al., Cell 56*:313-321 (1989)); electroporation of cells or embryos (Lo, *Mol. Cell. Biol. 3*:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer *et al., Science 259*:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano *et al., Cell 57*:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol. 115*:171-229 (1989), which is incorporated by reference herein in its entirety.

[1135] Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell *et al., Nature 380*:64-66 (1996); Wilmut *et al., Nature 385*:810-813 (1997)).

[1136] The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, i.e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko *et al., Proc. Natl. Acad. Sci. USA 89*:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred.

[1137] Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal

sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu *et al.* (Gu *et al., Science 265*:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. The contents of each of the documents recited in this paragraph is herein incorporated by reference in its entirety.

[1138] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

[1139] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

[1140] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of KGF-2 polypeptides, studying conditions and/or disorders associated with aberrant KGF-2 expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

EXAMPLE 47

KGF-2 Knock-Out Animals

[1141] Endogenous KGF-2 gene expression can also be reduced by inactivating or "knocking out" the KGF-2 gene and/or its promoter using targeted homologous recombination. (E.g., see Smithies *et al.*, *Nature 317*:230-234 (1985); Thomas & Capecchi, *Cell 51*:503-512 (1987); Thompson *et al.*, *Cell 5*:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

[1142] In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the KGF-2 polypeptides. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

[1143] Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[1144] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while

allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

[1145] Knock-out animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of KGF-2 polypeptides, studying conditions and/or disorders associated with aberrant KGF-2 expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

EXAMPLE 48

Construction of KGF-2 mutants

[1146] To create point mutants, the indicated primers were used in PCR reactions using standard conditions well known to those skilled in the art. The resulting products were restricted with either Nde and Asp718 and cloned into pHE4; or with BamHI and Xba and cloned into pcDNA3; as indicated. Any of the described KGF-2 variants can be produced in other vectors, or by themselves, using methods well known in the art.

pHE4:KGF2:R80-S208 was constructed using following primers:

5' primer: CCGGC CATATG CGTAAACTGTTCTCTTTCACC (SEQ ID NO:151)

3' primer: CCGGC GGTACC TTATTATGAGTGTACCACCATTGG (SEQ ID NO:152)

pHE4:KGF2:A63-S208(R68G) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTCGTTC (SEQ ID NO:153)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:154)

pHE4:KGF2:A63-S208(R68S) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTCGTTC (SEQ ID NO:155)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:156)

pHE4:KGF2:A63-S208(R68A) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTCGTTC (SEQ ID NO:157)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:158)

pHE4:KGF2:A63-S208(R78R80K81A) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTCGTTC (SEQ ID NO:159)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:160)

pcDNA3:KGF2(K136137139144A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:161)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:162)

pcDNA3:KGF2(K151153R155A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:163)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:164)

pcDNA3:KGF2(R174K183A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:165)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:166)

pcDNA3:KGF2(R187R188A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:167)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:168)

pHE4:KGF2.A63(K136137139144A) was constructed using the following primers:

5' primer: GATCGCCATATGGCTGGTCGTCACGTTCGTTC (SEQ ID NO:169)

3' primer: GATCGCGGTACCTTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:170)

pHE4:KGF2.A63(K151153R155A) was constructed using the following primers:

5' primer: GATCGCCATATGGCTGGTCGTCACGTTCGTTC (SEQ ID NO:171)

3' primer: GATCGCGGTACCTTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:172)

EXAMPLE 49

Use of KGF-2 for Treating and/or Preventing Infertility

[1147] Implantation is the single most critical factor in a successful pregnancy and is clinically and economically important. In humans, the greatest fraction of the 70% loss in embryonic life occurs at implantation. The mouse is the model of choice for studying mammalian implantation. Three essential cell lineages differentiate and divide in the peri-implantation mouse embryo: embryonic,

placental and yolk sac precursors. Fibroblast growth factor (FGF)-4 is essential for development of all three cell lineages.

[1148] It has been found, using a 'transient transgenic' approach to deliver gain-of-function and loss-of-function (dominant negative) FGF receptor genes, that endogenous FGF signaling is necessary for cell division of all stem cells for the embryo and placenta lineages in the mouse embryo starting at the fifth cell division two days before implantation.

[1149] Interestingly, it has been found that null mutant for *fgfr-2* and *fgf4* die in uteri within a day after implantation and the ICM dies. Before the embryo implants into the uterus cells in the embryonic lineage and in the placental lineage require FGF to continue proliferating.

[1150] It is possible that one or several of the other 19 FGF ligand is expressed transiently in the mouse preimplantation embryo and this ligand delays the effect of the *fgfr-2* and *fgf4* null mutants until after implantation. We have tested for six FGF ligand using RT-PCR. To date, KGF-2 and FGF-8 are the only FGF ligands, besides FGF-4, detected in the preimplantation embryo. KGF-2 mRNA is detected in the embryo after the two cell stage and through early post-implantation.

[1151] *KGF-2* null mutants suggest that KGF-2 is not essential for survival during the expression of KGF-2 in peri-implantation mouse embryos (Min et al., 1998; Sekine et al., 1999). However, other FGF family members may compensate or be redundant for KGF-2 during peri-implantation embryonic development. Many redundant genetic effects have been observed during analysis of null mutants in mice and compensation within a gene family has also been observed (Thomas et al., 1995; Stein et al., 1994). KGF-2 may be more important in early development than is suggested by the *KGF-2* null mutants.

[1152] The best way to detect whether KGF-2 may have role in early development at a time when the null mutants suggest no essential function, is to do gain-of-function experiments. These experiments test whether KGF-2 has an influence on growth of perimplantation embryos (Rappolee et al., 1994), on the

placental/trophoblast cells in blastocyst outgrowths (Chai et al., 1998) and in endoderm lineage cells in inner call mass (ICM) outgrowths (Rappolee et al., 1994). Loss-of-function tests can be done in a limited way by use of antisense oligonucleotides (Rappolee et al., 1992) or blocking antibodies (LaFleur et al., 1996). It is known that the embryos undergo size regulation, large positive and negative changes in cell number are homoeostatically regulated, soon after implantation (Rappolee, 1998). This suggests that small, sublethal KGF-2-dependent effects might be totally missed in the *KGF-2* null mutants. Loss- and gain-of-function experiments are use to test peri-implantation mouse embryos for the effects of KGF-2.

[1153] To date, the detection of mRNA for a growth factor in the preimplantation mouse embryo has universally led to detection of the corresponding protein. (Rappolee et al., 1998, 1992, 1994; reviewed in Rappolee 1998, 1999). To determine whether KGF-2 protein is present (and where) in embryos where KGF-2 mRNA was detected, an antibody to KGF-2 suitable for immunocytochemistry is used.

[1154] One skilled in the art could easily modify the exemplified studies to test the activity of any KGF-2 polypeptide, including full length and mature KGF-2, KGF-2 Δ28, KGF-2 Δ33, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 50

Detection of KGF-2 in a clinical sample

[1155] Purified Goat PAb is diluted to 2 μg/ml in the coating buffer (0.05 M $NaHCO_3$, Ph 9.5). 100 μl diluted antibody is added per well to an Immuno 4 microplate. The microplate is stored overnight at 4°C. The antibody solution is

decanted from the plate. 200 μl of blocking buffer (1% dry milk (BioRad) in coating buffer) is added to each well. The plate is allowed to incubate at room temperature for 2 hours. The blocking buffer is decanted from the plate. The plate is vacuum aspirated and allowed to dry completely in a vacuum chamber at 32°C for 1.5 hours. The plate is removed from the vacuum chamber and sealed in a mylar pouch with 3 desiccant packs. The plate is stored at 4°C until ready to be used.

[1156] KGF-2 is diluted to 16 ng/ml with diluent 1 (0.1% Tween 20, 1xPBS, 1% BSA, and 0.001% Thimerosal), then a subsequent 2.5x dilution is made for the next 7 dilutions. The concentration range from 16 ng/ml to 0.026 ng/ml is used as the standard. The background wells consist of diluent without protein.

[1157] The unknown samples are diluted 10X, 50X, and 250X with diluent 1. 100 μl per well of the serial diluted standard solution and the unknown samples are added to the coated ELISA plate. The plate is stored at 4°C overnight.The solutions are decanted from the plate. The plate is washed with washing buffer (0.1% Tween 20 and 1x PBS) five times, using the Wheaton Instrument set at 1.6 ml (each well receives 200 μl per wash). 15 seconds of incubation of washing buffer is allowed between each wash.

[1158] The detector, biotinylated chicken anti-KGF-2 is diluted to 0.5 μg/ml in diluent 1. 100 μl of the diluted detector is added to each well. The plate is incubated for 2 hours at room temperature. The solution is decanted and the plate is washed with washing buffer 5 times, as before. 15 seconds of incubation time is allowed between each wash.

[1159] Peroxidase streptavidin is diluted to 1:2000 in diluent 1. 100 μl per well of the diluted peroxidase streptavidin is added to the plate and allowed to incubate at room temperature for 1 hour. The plate is decanted and washed with washing buffer five times. 15 seconds of incubation of washing buffer is allowed between each wash. The plate is not allowed to dry.

[1160] Equal amounts of room temperature TMB peroxidase substrate and the peroxidase solution B (from the TMB Peroxidase Microwell Substrate System,

KPL) are mixed. 100 μl of the mixed solution is added to each well and the color is allowed to develop at room temperature for 10 minutes. The color development is stopped by adding 50 μl of 1M H_2SO_4 to each well. The plate is read at 450 nm.

EXAMPLE 51

Construction of E. coli optimized truncated KGF-2

[1161] In order to increase expression levels of a truncated KGF-2 in an E. coli expression system, the codons of the gene were optimized to highly used E. coli codons.

[1162] For example, the following construct, termed pHE4:KGF-2.A63-S608, was made.

5' CATATGGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGT
GACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAA
AATCGAAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTG
CCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTTGTT
GCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGA
AGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCT
GAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATT
TAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGG
AAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACA
CCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAATAAGGTACC
3' (SEQ ID NO:173)

[1163] A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:173 was deposited as ATCC Deposit No. PTA-2183 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

[1164] Another construct, termed pHE4:KGF-2.A63-S208 cod.opt, was constructed using the following primers:

sense 5' GACTACATATGGCTGGTCGTCACGTTCGTTCTTACAACC ACCTGCA GG3' (SEQ ID NO:174)

antisense 5' CTAGTCTCTAGATTATTATGAGTGTACAACCATCG GCAGGAAGTGAG 3' (SEQ ID NO:175)

[1165] The nucleotide sequence of the pHE4:KGF-2.A63-208 cod.opt is as follows:

5' ATGGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGTG ACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAA ATCGAAAAGAACGGTAAAGTTTCTGGTACCAAGAAAGAAAACTGC CCGTACTCTATCCTGGAAATCACCTCCGTTGAAATCGGTGTTGTAG CCGTTAAAGCCATCAACTCCAACTATTACCTGGCCATGAACAAAAA GGGTAAACTGTACGGCTCTAAAGAATTCAACAACGACTGCAAACT GAAAGAACGTATCGAAGAGAACGGTTACAACACCTACGCATCCTT CAACTGGCAGCACAACGGTCGTCAGATGTACGTTGCACTGAACGGT AAAGGCGCTCCGCGTCGCGGTCAGAAAACCCGTCGCAAAAACACC TCTGCTCACTTCCTGCCGATGGTTGTACACTCATAATAA 3' (SEQ ID NO:176)

[1166] A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:176 was deposited as ATCC Deposit No. PTA-2184 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

[1167] Both constructs described in this example are useful in the production of KGF-2 polypeptides, for example, as described in Example 13. Nucleotides 4 to 444 of SEQ ID NO:173 and nucleotides 1 to 441 of SEQ ID NO:176 encode amino acids 63 to 208 of SEQ ID NO:2, plus an N-terminal methionine.

EXAMPLE 52

Stimulation of pulmonary epithelial cells

[1168] Rats receiving an intratracheal dose of KGF-2Δ28 were injected with BrdU hours later, and BrdU$^+$ alveolar cells quantified. A single IT infusion at a dose of 0.1, 0.3 or 1 mg/kg induced a significant 10-fold increase in the number of BrdU$^+$ cells per microscopic field compared to controls. Histologic evaluation of H & E stained sections revealed no fibrosis, but showed alveolar hyperplasia characterized by the "knobby proliferation" associated with Type II pneumocyte cell division. In a monkey study, following administration of 1 mg/kg IT KGF-2Δ28, the number of BrdU positive alveolar cells was significantly increased over controls (65 BrdU$^+$ cells/field v. 4). In addition, bronchial epithelial cells exhibited a robust proliferative response following infusion of KGF-2 Δ28.

[1169] The studies described in this example test activity in KGF-2 Δ28 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ33, and polypeptide comprising amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

[1170]

EXAMPLE 53

Prophylactic treatment of mucositis

[1171] KGF-2Δ33 was shown to be protective in studies involving radiation-induced mortality in mice, cyclophosphamide-induced bladder mucositis in rats, indomethacin-induced intestinal mucositis in rats and LPS-induced endotoxemia in mice. Pretreatment of mice with 1 mg/kg, intravenously of KGF-2Δ33 for 3 days prior to exposure to a lethal split dose of whole body irradiation significantly

($p<0.03$) reduced mortality compared to the control group (30% vs 90% mortality). In experimental cylcophosphamide-induced cystitis, a single IV dose of KGF-2Δ33 (1mg/kg), injected 24 hours before cyclophoshamide, significantly ($p<0.05$) lowered cylcophosphamide-induced bladder wet weight, a surrogate marker of edema, 73%. Based on histologic evaluation of edema, hemorrhage, inflammation and ulceration, KGF-2Δ33 treatment reduced the histologic score to 2.2 compared with 7.3 for the control group. In acute indomethacin-induced intestinal injury, one IV injection of KGF-2Δ33 (1 mg/kg) 3 days before intitiaion of treatment with indomethacin, significantly ($0<0.05$) reduced indomethacin-mediated pathology 36-49%, as measured by the reduction of intestinal ulceration, inflammatory score and edema. In a murine model of sub-lethal endotoxic shock, KGF-2Δ33 (10 mg/kg, IP) adnubustered 10 minutes prior to LPS injection, significantly ($p<0.001$) reduced elevated levels of serum TNF from a control value of 7600 pg/ml to 1400 pg/ml, and lowered serum IL-1 and IL-6 levels almost 50%. KGF-2Δ33 can thus be used to treat mucositis in patients undergoing cancer chemo- or radio-therapy.

[1172] The studies described in this example test activity in KGF-2 Δ33 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ28, and polypeptide comprising encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

[1173] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples.

[1174] Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, within the scope of the appended claims, the invention may be practiced otherwise than as particularly described.

[1175] The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

Applicant's or agent's file reference number 1488.036PC0P	International application No. (TO BE ASSIGNED)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 4, line 11.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution
American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
December 16, 1994	75977

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA Plasmid, 366885A

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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Applicant's or agent's file reference number 1488.036PC0P	International application No. (TO BE ASSIGNED)

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United States of America

Date of deposit	Accession Number
September 29, 1994	75901

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA Plasmid, 366,885

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Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
January 9, 1998	209575

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA Plasmid pHEKGF-2delta33

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United States of America

Date of deposit	Accession Number
June 30, 1999	PTA-290

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA Plasmid pVGI-0: KGF2 (F.L.) (Ref. PF155)

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 429, line 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

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Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
June 30, 1999	PTA-289

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

DNA Plasmid pVGI-0:Δ33 KGF2 (Ref. PF155)

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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Applicant's or agent's file reference number 1488.036PC0P	International application No. PCT/US00/18328

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(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 442, line 24.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

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10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
03 July 2000	PTA-2183

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

(DNA Plasmid (Human): pHE4.KGF-2.A63-S208)

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

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United States of America

Date of deposit	Accession Number
03 July 2000	PTA-2184

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

(DNA Plasmid (Human): pHE4.KGF-2.A63-S208c.o.)

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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WHAT IS CLAIMED IS:

1. A method for treating inflammation comprising administering to a patient in need thereof a thereapeutically effective amount of KGF-2Δ28.

2. The method of claim 1, wherein said KGF-2Δ28 is administered via gene thereapy.

3. A method of stimulating the growth of pulmonary epithelial cells, comprising contacting said cells with KGF-2Δ28.

4. The method of claim 3, wherein said cells comprise an isolated polynucleotide encoding KGF-2Δ28.

5. A method of preventing mucositis, comprising administered to an individual a prophylactically effective amount of KGF-2Δ33.

```
      ATGTGGAAATGGATACTGACACATTGTGCCTCAGCCTTTCCCCACCTGCCCGGCTGCTGC
1     ---------+---------+---------+---------+---------+---------+    60
      TACACCTTTACCTATGACTGTGTAACACGGAGTCGGAAAGGGGTGGACGGGCCGACGACG

        M  W  K  W  I  L  T  H  C  A  S  A  F  P  H  L  P  G  C  C

      TGCTGCTGCTTTTTGTTGCTGTTCTTGGTGTCTTCCGTCCCTGTCACCTGCCAAGCCCTT
61    ---------+---------+---------+---------+---------+---------+   120
      ACGACGACGAAAAACAACGACAAGAACCACAGAAGGCAGGGACAGTGGACGGTTCGGGAA

        C  C  C  F  L  L  L  F  L  V  S  S  V  P  V  T  C  Q  A  L

      GGTCAGGACATGGTGTCACCAGAGGCCACCAACTCTTCTTCCTCCTCCTTCTCCTCTCCT
121   ---------+---------+---------+---------+---------+---------+   180
      CCAGTCCTGTACCACAGTGGTCTCCGGTGGTTGAGAAGAAGGAGGAGGAAGAGGAGAGGA

        G  Q  D  M  V  S  P  E  A  T  N  S  S  S  S  S  F  S  S  P

      TCCAGCGCGGGAAGGCATGTgCGGAGCTACAATCACCTTCAAGGAGATGTCCGCTGGAGA
181   ---------+---------+---------+---------+---------+---------+   240
      AGGTCGCGCCCTTCCGTACAcGCCTCGATGTTAGTGGAAGTTCCTCTACAGGCGACCTCT

        S  S  A  G  R  H  V  R  S  Y  N  H  L  Q  G  D  V  R  W  R
```

MATCH WITH FIG. 1B

FIG.1A

MATCH WITH FIG. 1A

```
     AAGCTATTCTCTTTCACCAAGTACTTTCTCAAGATTGAGAAGAACGGGAAGGTCAGCGGG
241  ---------+---------+---------+---------+---------+---------+  300
     TTCGATAAGAGAAAGTGGTTCATGAAAGAGTTCTAACTCTTCTTGCCCTTCCAGTCGCCC

      K  L  F  S  F  T  K  Y  F  L  K  I  E  K  N  G  K  V  S  G

     ACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTT
301  ---------+---------+---------+---------+---------+---------+  360
     TGGTTCTTCCTCTTGACGGGCATGTCGTAGGACCTCTATTGTAGTCATCTTTAGCCTCAA

      T  K  K  E  N  C  P  Y  S  I  L  E  I  T  S  V  E  I  G  V

     GTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAACTC
361  ---------+---------+---------+---------+---------+---------+  420
     CAACGGCAGTTTCGGTAATTGTCGTTGATAATGAATCGGTACTTGTTCTTCCCCTTTGAG

      V  A  V  K  A  I  N  S  N  Y  Y  L  A  M  N  K  K  G  K  L

     TATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGA
421  ---------+---------+---------+---------+---------+---------+  480
     ATACCGAGTTTTCTTAAATTGTTACTGACATTCGACTTCCTCTCCTATCTCCTTTTACCT

      Y  G  S  K  E  F  N  N  D  C  K  L  K  E  R  I  E  E  N  G
```

MATCH WITH FIG. 1C

FIG.1B

MATCH WITH FIG. 1B

```
     TACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTG
481  ---------+---------+---------+---------+---------+---------+  540
     ATGTTATGGATACGTAGTAAATTGACCGTCGTATTACCCTCCGTTTACATACACCGTAAC

      Y  N  T  Y  A  S  F  N  W  Q  H  N  G  R  Q  M  Y  V  A  L

     AATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCAC
541  ---------+---------+---------+---------+---------+---------+  600
     TTACCTTTTCCTCGAGGTTCCTCTCCTGTCTTTTGTGCTTCCTTTTTGTGGAGACGAGTG

      N  G  K  G  A  P  R  R  G  Q  K  T  R  R  K  N  T  S  A  H

     TTTCTTCCAATGGTGGTACACTCATAG
601  ---------+---------+-------  627
     AAAGAAGGTTACCACCATGTGAGTATC

      F  L  P  M  V  V  H  S  *
```

FIG.1C

```
          1                                                    50
FGF4      MS.GPGTAAV ALLPAVLLAL LA........ .PWAGRGGAA APTAPNGTLE
FGF6      MSRGAGRLQG TLWALVFLGI LV........ .GMVVPSPAG TR.ANNTLLD
FGF5      .......MSL SFLLLLFFSH LILSAWAHGE KRLAPKGQPG PAATDRNPIG
FGF1      .......... .......... .......... .......... ..........
FGF2      .......... .......... .......... .......... ..........
FGF9      .......... .......... .......... ..MAPLGEVG NYFGVQDAVP
FGF7      .......... ......MHKW ILTWILPTLL .....YRSCF HIICLVGTIS
KGF2      .......... ......MWKW ILTHCASAFP HLPGCCCCCF LLLFLVSSVP
FGF3      .......... .......... .......... .......MGL IWLLLLSLLE
FGF8      MGSPRSALSC LLLHLLVLCL QAQVRSAAQK RGPGAGNPAD TLGQGHEDRP

          51                                                   100
FGF4      AELERRWESL VALSLARLPV AA..QPKEAA VQSGAGDY.. ...LLGIKRL
FGF6      S...RGWGTL LSRSRAGLAG EI......AG VNWESG.Y.. ...LVGIKRQ
FGF5      SSSRQSSSSA MSSSSASSSP AASLGSQGSG LEQSSFQW.. ...SPSGRRT
FGF1      ......MAEG EITTFTALTE KFN...LPPG .......N.. ...YK...KP
FGF2      ......MAAG SITTLPALPE DGGSGAFPPG .......H.. ...FK...DP
FGF9      FGNVPVLPVD SPVLLSDHLG QSEAGGLPRG PAVTDLDH.. ...LKGILRR
FGF7      LACNDMTPEQ M...ATNVNC ......SSPE RHTRSYDY.. ...MEGGDIR
KGF2      VTCQALGQDM VSPEATNSSS SSFSSPSSAG RHVRSYNH.. ...LQ.GDVR
FGF3      PGWPAAGPGA .......... ...RLRRDAG GRGGVYEH.. ...L.GGAPR
FGF8      FGQRSRAGKN FTNPAPNYPE EGSKEQRDSV LPKVTQRHVR EQSLVTDQLS
```

MATCH WITH FIG. 2B

FIG. 2A

MATCH WITH FIG. 2A

```
        101                                                        150
FGF4    RRL.....YC NVGIGFHLQA LPDGRIGGAH ADT.RDSLLE LSPVERGV.V
FGF6    RRL.....YC NVGIGFHLQV LPDGRISGTH EEN.PYSLLE ISTVERGV.V
FGF5    GSL.....YC RVGIGFHLQI YPDGKVNGSH EAN.MLSVLE IFAVSQGI.V
FGF1    KLL.....YC SNG.GHFLRI LPDGTVDGTR DRSDQHIQLQ LSAESVGE.V
FGF2    KRL.....YC KNG.GFFLRI HPDGRVDGVR EKSDPHIKLQ LQAEERGV.V
FGF9    RQL.....YC R.T.GFHLEI FPNGTIQGTR KDHSRFGILE FISIAVGL.V
FGF7    VRR.....LF CRT.QWYLRI DKRGKVKGTQ EMKNNYNIME IRTVAVGI.V
KGF2    WRK.....LF SFT.KYFLKI EKNGKVSGTK KENCPYSILE ITSVEIGV.V
FGF3    RRK.....LY CAT.KYHLQL HPSGRVNGSL .ENSAYSILE ITAVEVGI.V
FGF8    RRLIRTYQLY SRTSGKHVQV LANKRINAMA EDGDPFAKLI VETDTFGSRV

        151                                                        200
FGF4    SIFGVASRFF VAMSSKGKLY G.SPFFTDEC TFKEILLPNN YNAYESYKYP
FGF6    SLFGVRSALF VAMNSKGRLY A.TPSFQEEC KFRETLLPNN YNAYESDLYQ
FGF5    GIRGVFSNKF LAMSKKGKLH A.SAKFTDDC KFRERFQENS YNTYASAIHR
FGF1    YIKSTETGQY LAMDTDGLLY G.SQTPNEEC LFLERLEENH YNTYISKKH.
FGF2    SIKGVCANRY LAMKEDGRLL A.SKCVTDEC FFFERLESNN YNTYRSRKY.
FGF9    SIRGVDSGLY LGMNEKGELY G.SEKLTQEC VFREQFEENW YNTYSSNLYK
FGF7    AIKGVESEFY LAMNKEGKLY A.KKECNEDC NFKELILENH YNTYAS....
KGF2    AVKAINSNYY LAMNKKGKLY G.SKEFNNDC KLKERIEENG YNTYAS....
FGF3    AIRGLFSGRY LAMNKRGRLY A.SEHYSAEC EFVERIHELG YNTYASRLYR
FGF8    RVRGAETGLY ICMNKKGKLI AKSNGKGKDC VFTEIVLENN YTALQNAKY.
```

MATCH WITH FIG. 2C

FIG. 2B

MATCH WITH FIG. 2B

```
        201                                                        250
FGF4    .......... GM......FI ALSKNGKTKK G..NRVSPTM KVTHFLPRL.
FGF6    .......... GT......YI ALSKYGRVKR G..SKVSPIM TVTHFLPRI.
FGF5    .......... TEKTGREWYV ALNKRGKAKR GCSPRVKPQH ISTHFLPRFK
FGF1    .......... ...AEKNWFV GLKKNGSCKR G..PRTHYGQ KAILFLPLPV
FGF2    .......... ...T..SWYV ALKRTGQYKL G..SKTGPGQ KAILFLPMSA
FGF9    HV........ ..DTGRRYYV ALNKDGTPRE G..TRTKRHQ KFTHFLPRPV
FGF7    .......AKW THNGGEM.FV ALNQKGIPVR G..KKTKKEQ KTAHFLPMAI
KGF2    .......FNW QHNGRQM.YV ALNGKGAPRR G..QKTRRKN TSAHFLPMVV
FGF3    TVSSTPGARR QPSAERLWYV SVNGKGRPRR G..FKTRRTQ KSSLFLPRVL
FGF8    .......... .....EGWYM AFTRKGRPRK G..SKTRQHQ REVHFMKRLP
```

```
        251                                                        300
FGF4    .......... .......... .......... .......... ..........
FGF6    .......... .......... .......... .......... ..........
FGF5    QSEQPELSFT VTVPEKKNPP SPIKSKIPLS APRKNTNSVK YRLKFRFG..
FGF1    SSD....... .......... .......... .......... ..........
FGF2    KS........ .......... .......... .......... ..........
FGF9    DPDKVPELYK DILSQS.... .......... .......... ..........
FGF7    T......... .......... .......... .......... ..........
KGF2    HS........ .......... .......... .......... ..........
FGF3    DHRDHEMVRQ LQSGLPRPPG KGVQPRRRRQ KQSPDNLEPS HVQASRLGSQ
FGF8    RGHHTTEQSL RFEFLNYPPF TRSLRGSQRT WAPEPR.... ..........
```

MATCH WITH FIG. 2D

FIG.2C

MATCH WITH FIG. 2C

	301
FGF4	.....
FGF6	.....
FGF5	.....
FGF1	.....
FGF2	.....
FGF9	.....
FGF7	.....
KGF2	.....
FGF3	LEASAH
FGF8	.....

FIG.2D

```
GGAATTCCGG GAAGAGAGGG AAGAAAACAA CGGCGACTGG GCAGCTGCCT CCACTTCTGA    60
CAACTCCAAA GGGATATACT TGTAGAAGTG GCTCGCAGGC TGGGGCTCCG CAGAGAGAGA   120
CCAGAAGGTG CCAACCGCAG AGGGGTGCAG ATATCTCCCC CTATTCCCCA CCCCACCTCC   180
CTTGGGTTTT GTTCACCGTG CTGTCATCTG TTTTTCAGAC CTTTTTGGCA TCTAACATGG   240
TGAAGAAAGG AGTAAAGAAG AGAACAAAGT AACTCCTGGG GGAGCGAAGA GCGCTGGTGA   300
CCAACACCAC CAACGCCACC ACCAGCTCCT GCTGCTGCGG CCACCCACGT CCACCATTTA   360
CCGGGAGGCT CCAGAGGCGT AGGCAGCGGA TCCGAGAAAG GAGCGAGGGG AGTCAGCCGG   420
CTTTTCCGAG GAGTTATGGA TGTTGGTGCA TTCACTTCTG GCCAGATCCG CGCCCAGAGG   480
GAGCTAACCA GCAGCCACCA CCTCGAGCTC TCTCCTTGCC TTGCATCGGG TCTTACCCTT   540
CCAGTATGTT CCTTCTGATG AGACAATTTC CAGTGCCGAG AGTTTCAGTA CA ATG       595
                                                          Met

TGG AAA TGG ATA CTG ACA CAT TGT GCC TCA GCC TTT CCC CAC CTG CCC     643
Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro

GGC TGC TGC TGC TGC TGC TTT TTG TTG CTG TTC TTG GTG TCT TCC GTC     691
Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val

CCT GTC ACC TGC CAA GCC CTT GGT CAG GAC ATG GTG TCA CCA GAG GCC     739
Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala

ACC AAC TCT TCT TCC TCC TCC TTC TCC TCT CCT TCC AGC GCG GGA AGG     787
Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg

CAT GTG CGG AGC TAC AAT CAC CTT CAA GGA GAT GTC CGC TGG AGA AAG     835
His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys

CTA TTC TCT TTC ACC AAG TAC TTT CTC AAG ATT GAG AAG AAC GGG AAG     883
Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys

GTC AGC GGG ACC AAG AAG GAG AAC TGC CCG TAC AGC ATC CTG GAG ATA     931
Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile

ACA TCA GTA GAA ATC GGA GTT GTT GCC GTC AAA GCC ATT AAC AGC AAC     979
Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn

TAT TAC TTA GCC ATG AAC AAG AAG GGG AAA CTC TAT GGC TCA AAA GAA    1027
Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu

TTT AAC AAT GAC TGT AAG CTG AAG GAG AGG ATA GAG GAA AAT GGA TAC    1075
Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr
```

FIG.3A

AAT ACC TAT GCA TCA TTT AAC TGG CAG CAT AAT GGG AGG CAA ATG TAT 1123
Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr

GTG GCA TTG AAT GGA AAA GGA GCT CCA AGG AGA GGA CAG AAA ACA CGA 1171
Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg

AGG AAA AAC ACC TCT GCT CAC TTT CTT CCA ATG GTG GTA CAC TCA 1216
Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser

TAGAGGAAGG CAACGTTTGT GGATGCAGTA AAACCAATGG CTCTTTTGCC AAGAATAGTG 1276

GATATTCTTC ATGAAGACAG TAGATTGAAA GGCAAAGACA CGTTGCAGAT GTCTGCTTGC 1336

TTAAAAGAAA GCCAGCCTTT GAAGGTTTTT GTATTCACTG CTGACATATG ATGTTCTTTT 1396

AATTAGTTCT GTGTCATGTC TTATAATCAA GATATAGGCA GATCGAATGG GATAGAAGTT 1456

ATTCCCAAGT GAAAAACATT GTGGCTGGGT TTTTTGTTGT TGTTGTCAAG TTTTTGTTTT 1516

TAAACCTCTG AGATAGAACT TAAAGGACAT AGAACAATCT GTTGAAAGAA CGATCTTCGG 1576

GAAAGTTATT TATGGAATAC GAACTCATAT CAAAGACTTC ATTGCTCATT CAAGCCTAAT 1636

GAATCAATGA ACAGTAATAC GTGCAAGCAT TTACTGGAAA GCACTTGGGT CATATCATAT 1696

GCACAACCAA AGGAGTTCTG GATGTGGTCT CATGGAATAA TTGAATAGAA TTTAAAAATA 1756

TAAACATGTT AGTGTGAAAC TGTTCTAACA ATACAAATAG TATGGTATGC TTGTGCATTC 1816

TGCCTTCATC CCTTTCTATT TCTTTCTAAG TTATTTATTT AATAGGATGT TAAATATCTT 1876

TTGGGGTTTT AAAGAGTATC TCAGCAGCTG TCTTCTGATT TATCTTTTCT TTTTATTCAG 1936

CACACCACAT GCATGTTCAC GACAAAGTGT TTTTAAAACT TGGCGAACAC TTCAAAAATA 1996

GGAGTTGGGA TTAGGGAAGC AGTATGAGTG CCCGTGTGCT ATCAGTTGAC TTAATTTGCA 2056

CTTCTGCAGT AATAACCATC AACAATAAAT ATGGCAATGC TGTGCCATGG CTTGAGTGAG 2116

AGATGTCTGC TATCATTTGA AAACATATAT TACTCTCGAG GCTTCCTGTC TCAAGAAATA 2176

GACCAGAAGG CCAAATTCTT CTCTTTCAAT ACATCAGTTT GCCTCCAAGA ATATACTAAA 2236

AAAAGGAAAA TTAATTGCTA AATACATTTA AATAGCCTAG CCTCATTATT TACTCATGAT 2296

TTCTTGCCAA ATGTCATGGC GGTAAAGAGG CTGTCCACAT CTCTAAAAAC CCTCTGTAAA 2356

TTCCACATAA TGCATCTTTC CCAAAGGAAC TATAAAGAAT TTGGTATGAA GCGCAACTCT 2416

FIG.3B

CCCAGGGGCT TAAACTGAGC AAATCAAATA TATACTGGTA TATGTGTAAC CATATACAAA 2476
AACCTGTTCT AGCTGTATGA TCTAGTCTTT ACAAAACCAA ATAAAACTTG TTTTCTGTAA 2536
ATTTAAAGAG CTTTACAAGG TTCCATAATG TAACCATATC AAAATTCATT TTGTTAGAGC 2596
ACGTATAGAA AAGAGTACAT AAGAGTTTAC CAATCATCAT CACATTGTAT TCCACTAAAT 2656
AAATACATAA GCCTTATTTG CAGTGTCTGT AGTGATTTTA AAAATGTAGA AAAATACTAT 2716
TTGTTCTAAA TACTTTTAAG CAATAACTAT AATAGTATAT TGATGCTGCA GTTTTATCTT 2776
CATATTTCTT GTTTTGAAAA AGCATTTTAT TGTTTGGACA CAGTATTTTG GTACAAAAAA 2836
AAAGACTCAC TAAATGTGTC TTACTAAAGT TTAACCTTTG GAAATGCTGG CGTTCTGTGA 2896
TTCTCCAACA AACTTATTTG TGTCAATACT TAACCAGCAC TTCCAGTTAA TCTGTTATTT 2956
TTAAAAATTG CTTTATTAAG AAATTTTTTG TATAATCCCA TAAAAGGTCA TATTTTTCCC 3016
ATTCTTCAAA AAAACTGTAT TTCAGAAGAA ACACATTTGA GGCACTGTCT TTTGGCTTAT 3076
AGTTTAAATT GCATTTCATC ATACTTTGCT TCCAACTTGC TTTTTGGCAA ATGAGATTAT 3136
AAAAATGTTT AATTTTTGTG GTTGGAATCT GGATGTTAAA ATTTAATTGG TAACTCAGTC 3196
TGTGAGCTAT AATGTAATGC ATTCCTATCC AAACTAGGTA TCTTTTTTTC CTTTATGTTG 3256
AAATAATAAT GGCACCTGAC ACATAGACAT AGACCACCCA CAACCTAAAT TAAATGTTTG 3316
GTAAGACAAA TACACATTGG ATGACCACAG TAACAGCAAA CAGGGCACAA ACTGGATTCT 3376
TATTTCACAT AGACATTTAG ATTACTAAAG AGGGCTATGT GTAAACAGTC ATCATTATAG 3436
TACTCAAGAC ACTAAAACAG CTTCTAGCCA AATATATTAA AGCTTGCAGA GGCCAAAAAT 3496
AGAAAACATC TCCCCTGTCT CTCCCACATT TCCCTCACAG AAAGACAAAA AACCTGCCTG 3556
GTGCAGTAGC TCACACCTGT AATCCCAGCA GTTTGGGAGA CTGTGGGAAG ATGGCTTGAG 3616
TCCAGGAGTT CTAGACAGGC CTGAGAAACC TAGTGAGACA TCCTTCTCTT AAACAAAACA 3676
AAACAAAACA AATGTAGCCA TGCGTGGTGG CATATACCTG TGGTCCCAAC TACTCAGGAG 3736
GCTGAAACGG AAGGATCTCT TGGGCCCCAG GAGTTTGAGG CTGCAGTGAG CTATAATCTT 3796
GCCATTGCAC TCCAGCCTGG GTGAAAAAGA GCCAGAAAGA AAGGAAAGAG AGAAAAGAGA 3856
AAAGAAAGAG AGAAAAGACA GAAAGACAGG AAGGAAGGAA GGAAGGAAGG AAGGAAGGAA 3916
GGAAGCAAGG AAAGAAGGAA GGAAGGAAAG AAGGGAGGGA AGGAAGGAGA GAGAAAGAAA 3976
GATTGTTTGG TAAGGAGTAA TGACATTCTC TTGCATTTAA AAGTGGCATA TTTGCTTGAA 4036

FIG.3C

ATGGAAATAG AATTCTGGTC CCTTTTGCAA CTACTGAAGA AAAAAAAAAG CAGTTTCAGC 4096

CCTGAATGTT GTAGATTTGA AAAAAAAAAA AAAAAAACTC GAGGGGGGGC CCGTACCCAA 4156

TTCGCCCTAT AGTGAGTCGT A 4177

FIG.3D

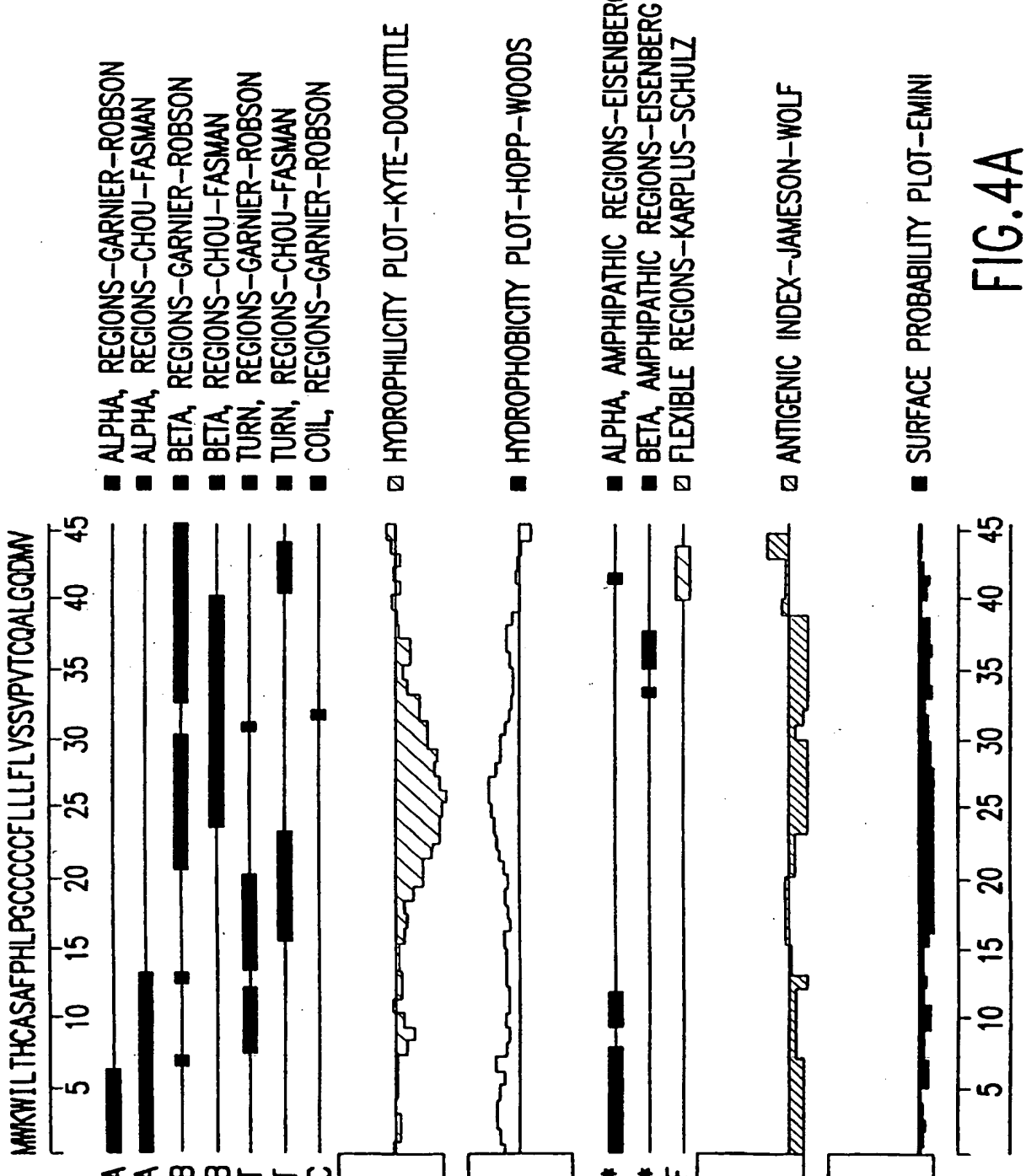

MWKWILTHCASAFPHLPGCCCCCFLLLFLVSSVPVTCQALGQDMV
5 10 15 20 25 30 35 40 45
A ALPHA, REGIONS-GARNIER-ROBSON
A ALPHA, REGIONS-CHOU-FASMAN
B BETA, REGIONS-GARNIER-ROBSON
B BETA, REGIONS-CHOU-FASMAN
T TURN, REGIONS-GARNIER-ROBSON
T TURN, REGIONS-CHOU-FASMAN
C COIL, REGIONS-GARNIER-ROBSON
3.38
0
-3.33
HYDROPHILICITY PLOT-KYTE-DOOLITTLE
3
0
-3.4
HYDROPHOBICITY PLOT-HOPP-WOODS
* ALPHA, AMPHIPATHIC REGIONS-EISENBERG
* BETA, AMPHIPATHIC REGIONS-EISENBERG
F FLEXIBLE REGIONS-KARPLUS-SCHULZ
3.4
0
ANTIGENIC INDEX-JAMESON-WOLF
6
1
SURFACE PROBABILITY PLOT-EMINI
5 10 15 20 25 30 35 40 45

FIG.4A

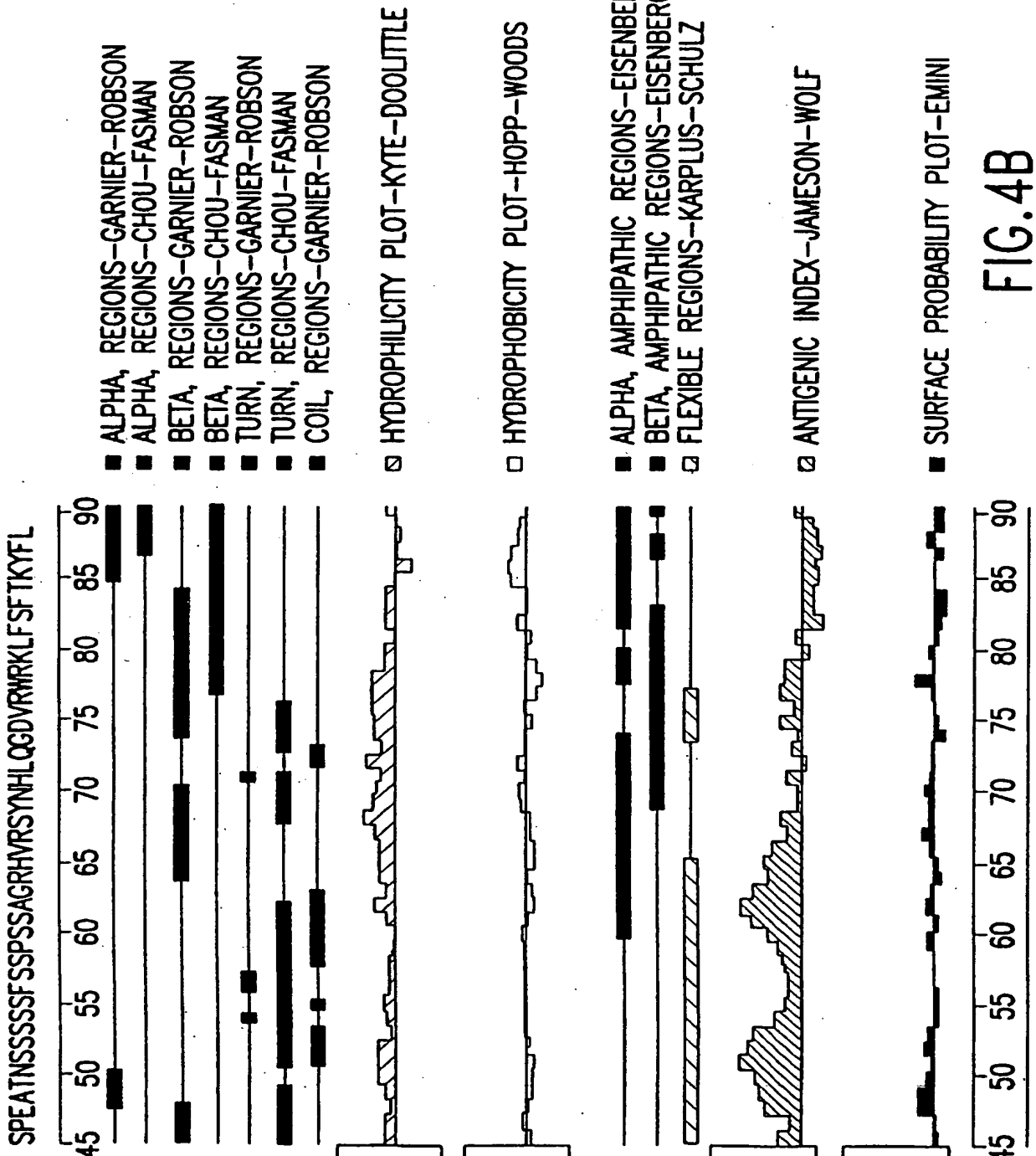

SPEATNSSSSFSSPSSAGRHVRSYNHLQGDVRWRKLFSFTKYFL
45 50 55 60 65 70 75 80 85 90
A ALPHA, REGIONS-GARNIER-ROBSON
A ALPHA, REGIONS-CHOU-FASMAN
B BETA, REGIONS-GARNIER-ROBSON
B BETA, REGIONS-CHOU-FASMAN
T TURN, REGIONS-GARNIER-ROBSON
T TURN, REGIONS-CHOU-FASMAN
C COIL, REGIONS-GARNIER-ROBSON
HYDROPHILICITY PLOT-KYTE-DOOLITTLE
3.38
0
-3.33
HYDROPHOBICITY PLOT-HOPP-WOODS
3
0
-3.4
* ALPHA, AMPHIPATHIC REGIONS-EISENBERG
* BETA, AMPHIPATHIC REGIONS-EISENBERG
F FLEXIBLE REGIONS-KARPLUS-SCHULZ
3.4
0
ANTIGENIC INDEX-JAMESON-WOLF
6
1
SURFACE PROBABILITY PLOT-EMINI
45 50 55 60 65 70 75 80 85 90

FIG.4B

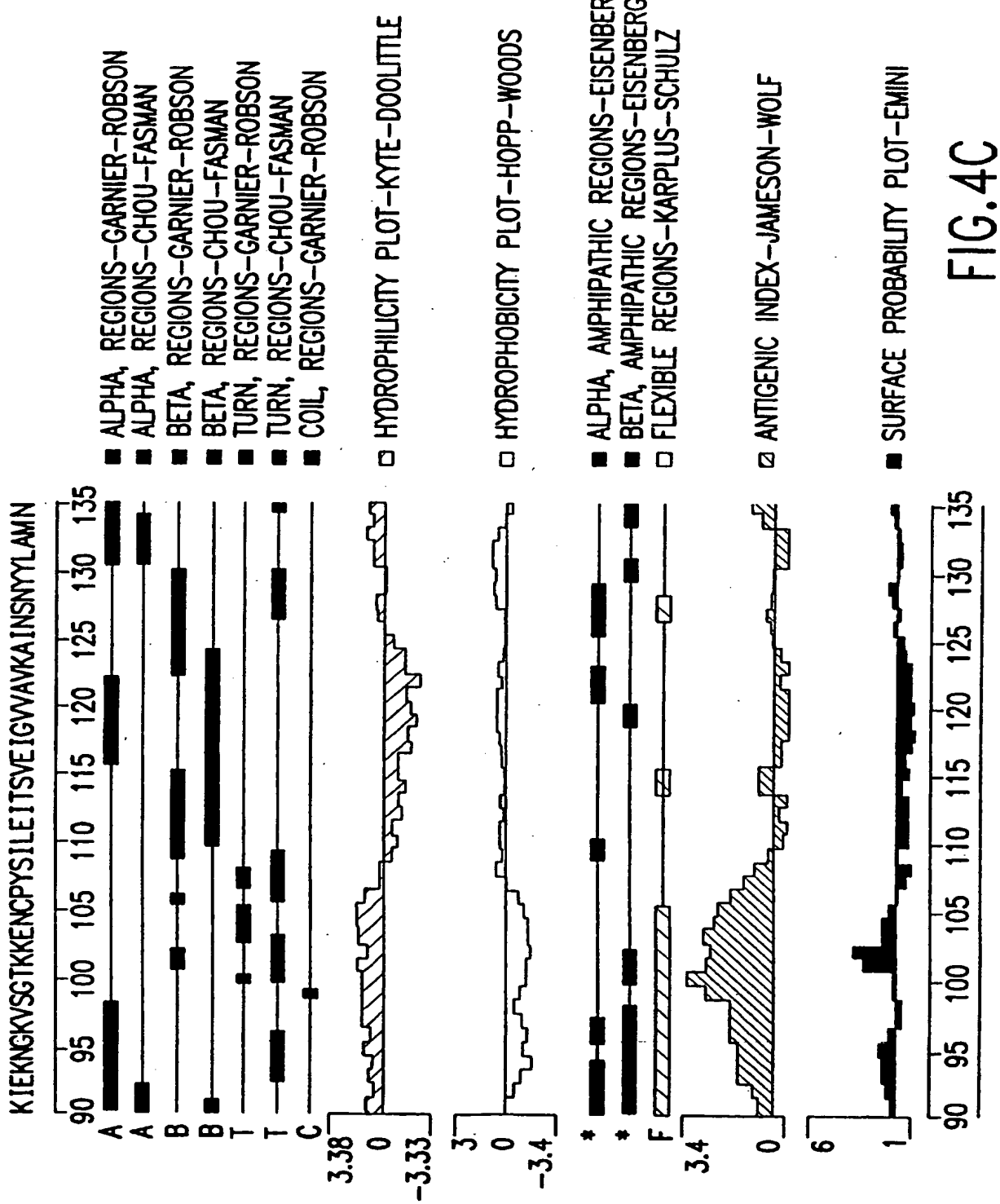

KIEKNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSNYYLAMN
90 95 100 105 110 115 120 125 130 135
A ALPHA, REGIONS-GARNIER-ROBSON
A ALPHA, REGIONS-CHOU-FASMAN
B BETA, REGIONS-GARNIER-ROBSON
B BETA, REGIONS-CHOU-FASMAN
T TURN, REGIONS-GARNIER-ROBSON
T TURN, REGIONS-CHOU-FASMAN
C COIL, REGIONS-GARNIER-ROBSON
HYDROPHILICITY PLOT-KYTE-DOOLITTLE
3.38
0
-3.33
HYDROPHOBICITY PLOT-HOPP-WOODS
3
0
-3.4
* ALPHA, AMPHIPATHIC REGIONS-EISENBERG
* BETA, AMPHIPATHIC REGIONS-EISENBERG
F FLEXIBLE REGIONS-KARPLUS-SCHULZ
ANTIGENIC INDEX-JAMESON-WOLF
3.4
0
SURFACE PROBABILITY PLOT-EMINI
6
1
90 95 100 105 110 115 120 125 130 135

FIG.4C

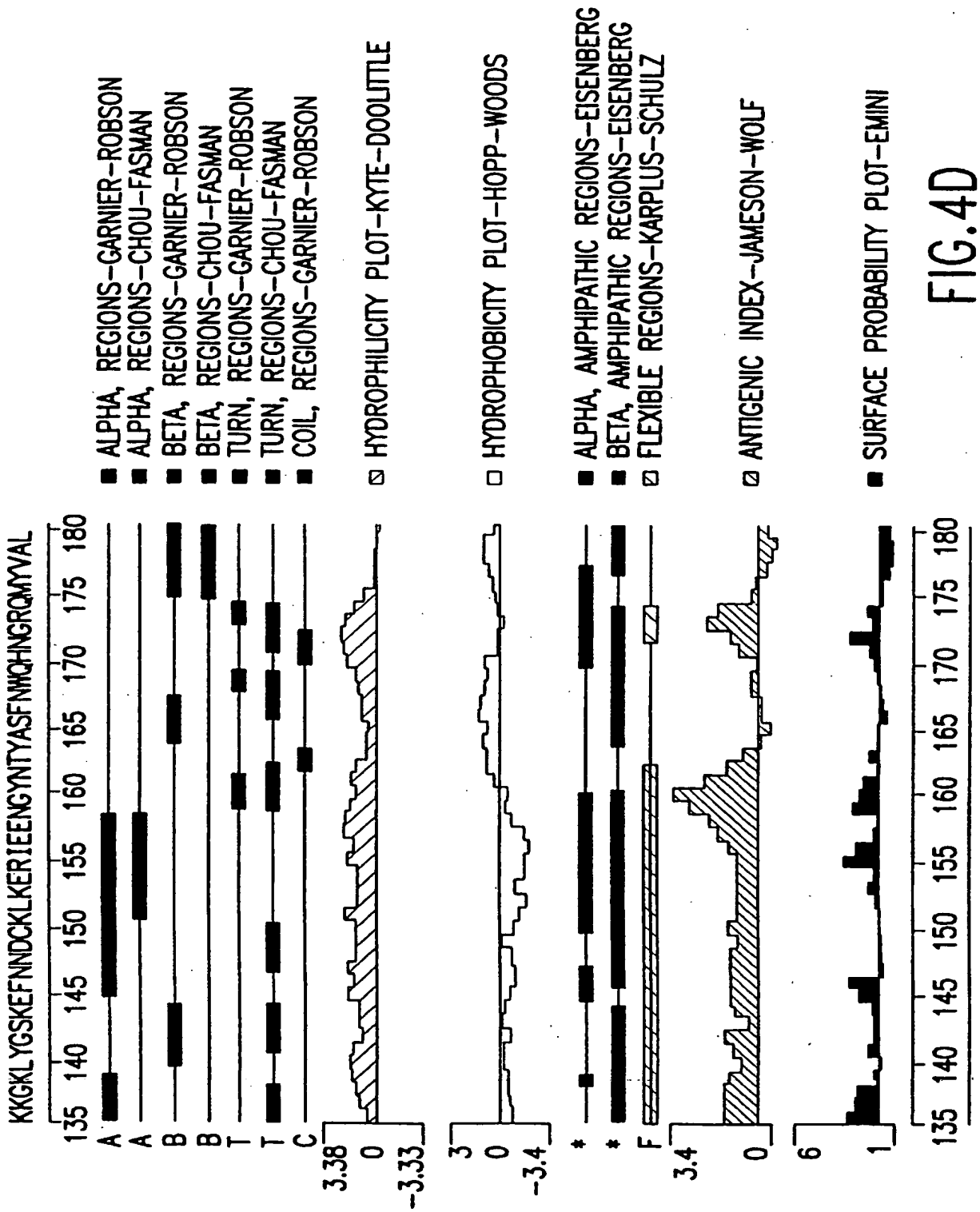

KKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVAL
135 140 145 150 155 160 165 170 175 180
A ALPHA, REGIONS-GARNIER-ROBSON
A ALPHA, REGIONS-CHOU-FASMAN
B BETA, REGIONS-GARNIER-ROBSON
B BETA, REGIONS-CHOU-FASMAN
T TURN, REGIONS-GARNIER-ROBSON
T TURN, REGIONS-CHOU-FASMAN
C COIL, REGIONS-GARNIER-ROBSON
HYDROPHILICITY PLOT-KYTE-DOOLITTLE
3.38
0
-3.33
HYDROPHOBICITY PLOT-HOPP-WOODS
3
0
-3.4
* ALPHA, AMPHIPATHIC REGIONS-EISENBERG
* BETA, AMPHIPATHIC REGIONS-EISENBERG
F FLEXIBLE REGIONS-KARPLUS-SCHULZ
ANTIGENIC INDEX-JAMESON-WOLF
3.4
0
SURFACE PROBABILITY PLOT-EMINI
6
1
135 140 145 150 155 160 165 170 175 180

FIG.4D

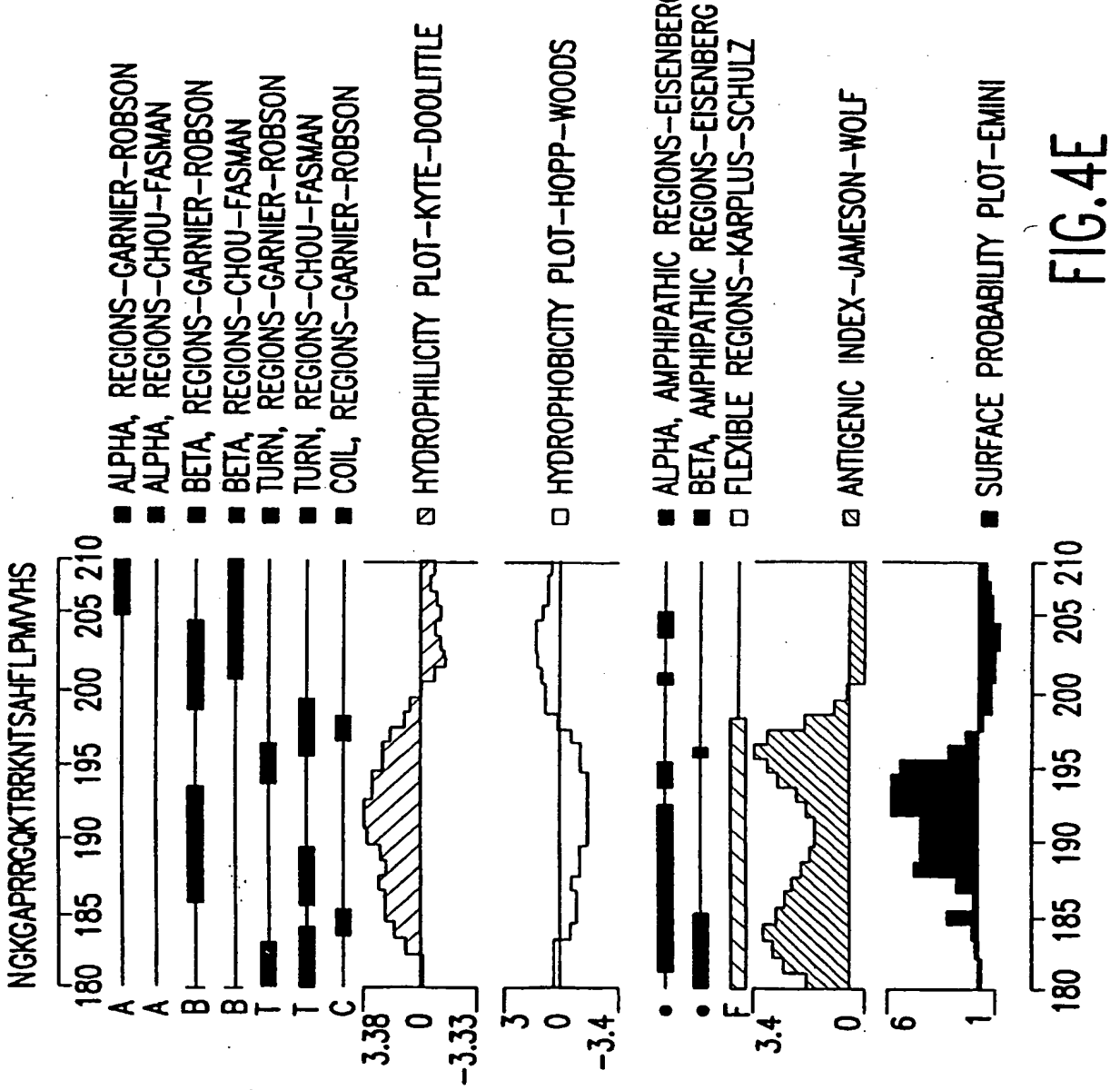

NGKGAPRRGQKTRRKNTSAHFLPMVVHS
180 185 190 195 200 205 210
A ALPHA, REGIONS-GARNIER-ROBSON
A ALPHA, REGIONS-CHOU-FASMAN
B BETA, REGIONS-GARNIER-ROBSON
B BETA, REGIONS-CHOU-FASMAN
T TURN, REGIONS-GARNIER-ROBSON
T TURN, REGIONS-CHOU-FASMAN
C COIL, REGIONS-GARNIER-ROBSON
3.38
0
-3.33
HYDROPHILICITY PLOT-KYTE-DOOLITTLE
3
0
-3.4
HYDROPHOBICITY PLOT-HOPP-WOODS
ALPHA, AMPHIPATHIC REGIONS-EISENBERG
BETA, AMPHIPATHIC REGIONS-EISENBERG
F FLEXIBLE REGIONS-KARPLUS-SCHULZ
3.4
0
ANTIGENIC INDEX-JAMESON-WOLF
6
1
SURFACE PROBABILITY PLOT-EMINI
180 185 190 195 200 205 210

FIG.4E

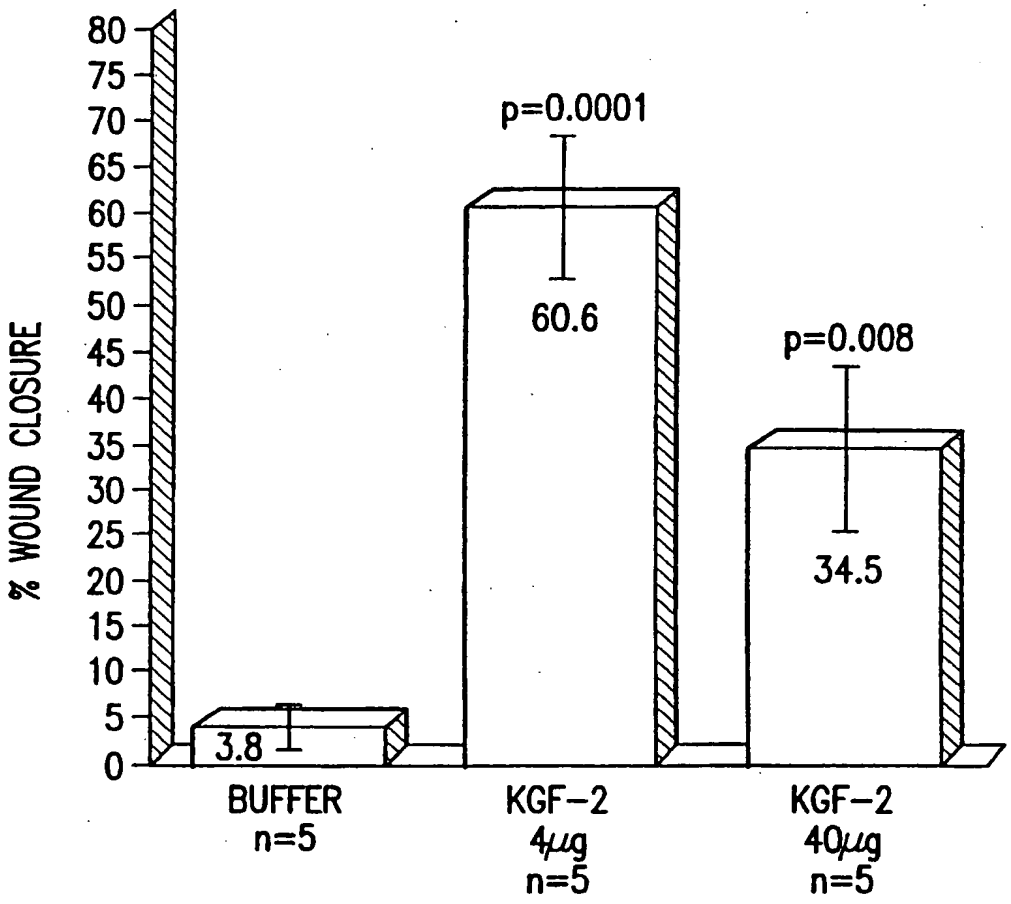

% WOUND CLOSURE
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
3.8
p=0.0001
60.6
p=0.008
34.5
BUFFER
n=5
KGF-2
4μg
n=5
KGF-2
40μg
n=5

FIG.5

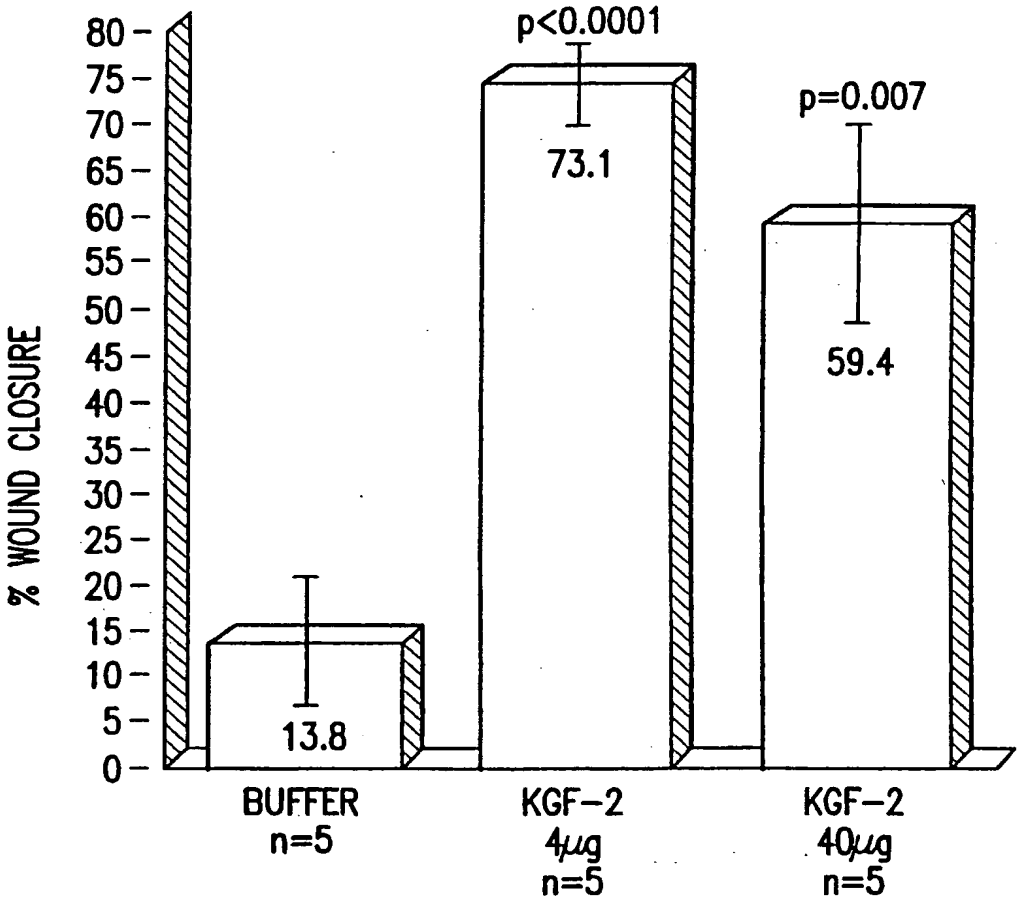

% WOUND CLOSURE
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
p<0.0001
73.1
p=0.007
59.4
13.8
BUFFER
n=5
KGF-2
4μg
n=5
KGF-2
40μg
n=5

FIG.6

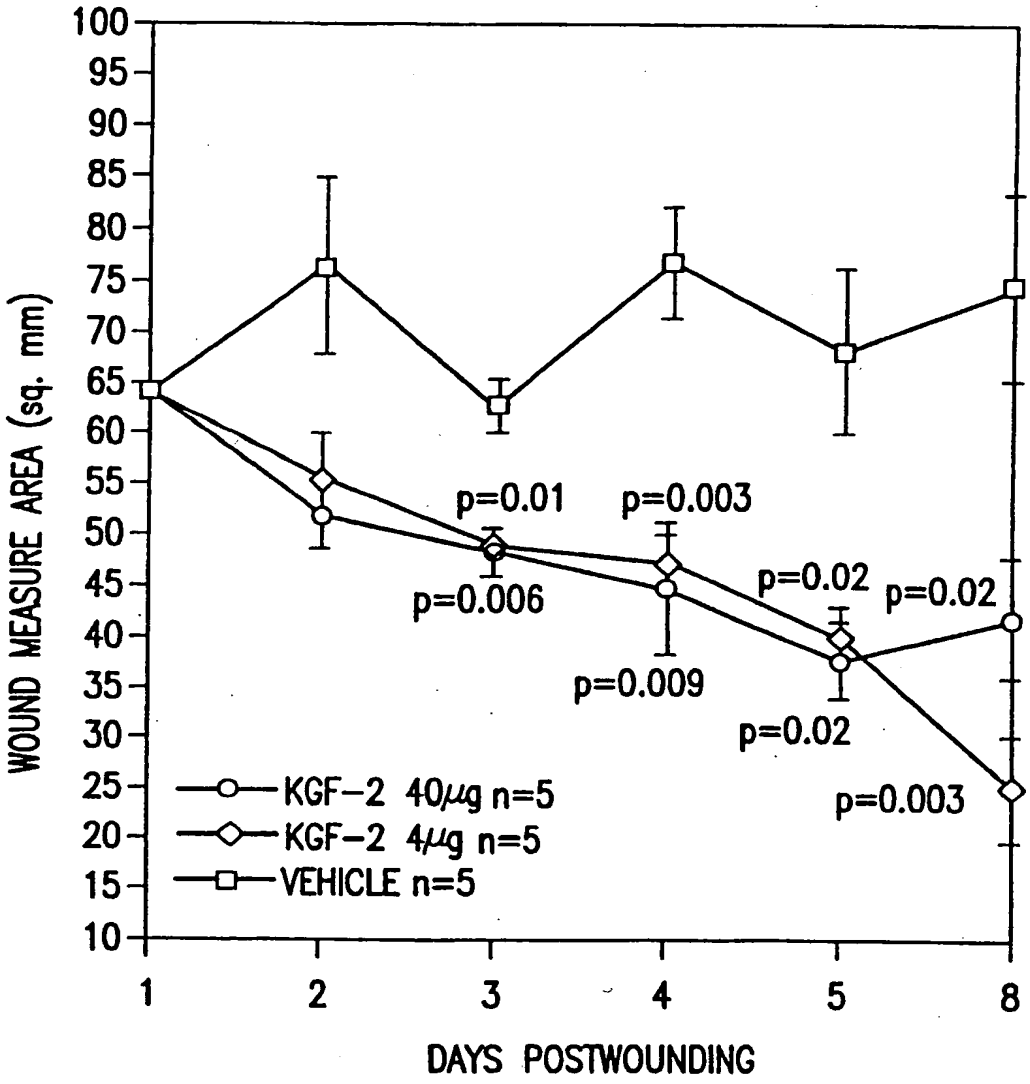

WOUND MEASURE AREA (sq. mm)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
1
2
3
4
5
8
DAYS POSTWOUNDING
p=0.01
p=0.003
p=0.006
p=0.02
p=0.02
p=0.009
p=0.02
p=0.003
KGF-2 40μg n=5
KGF-2 4μg n=5
VEHICLE n=5

FIG.7

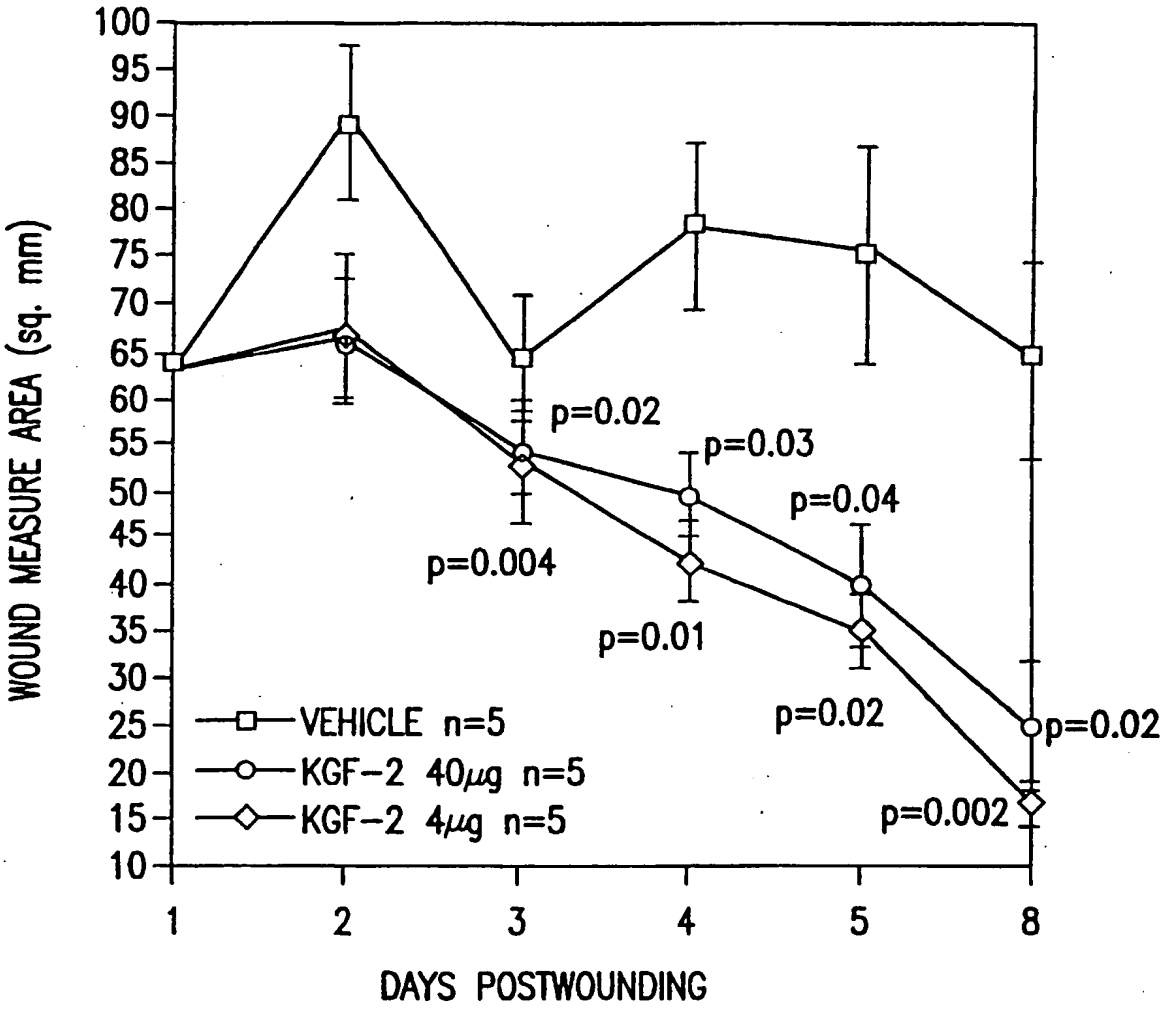
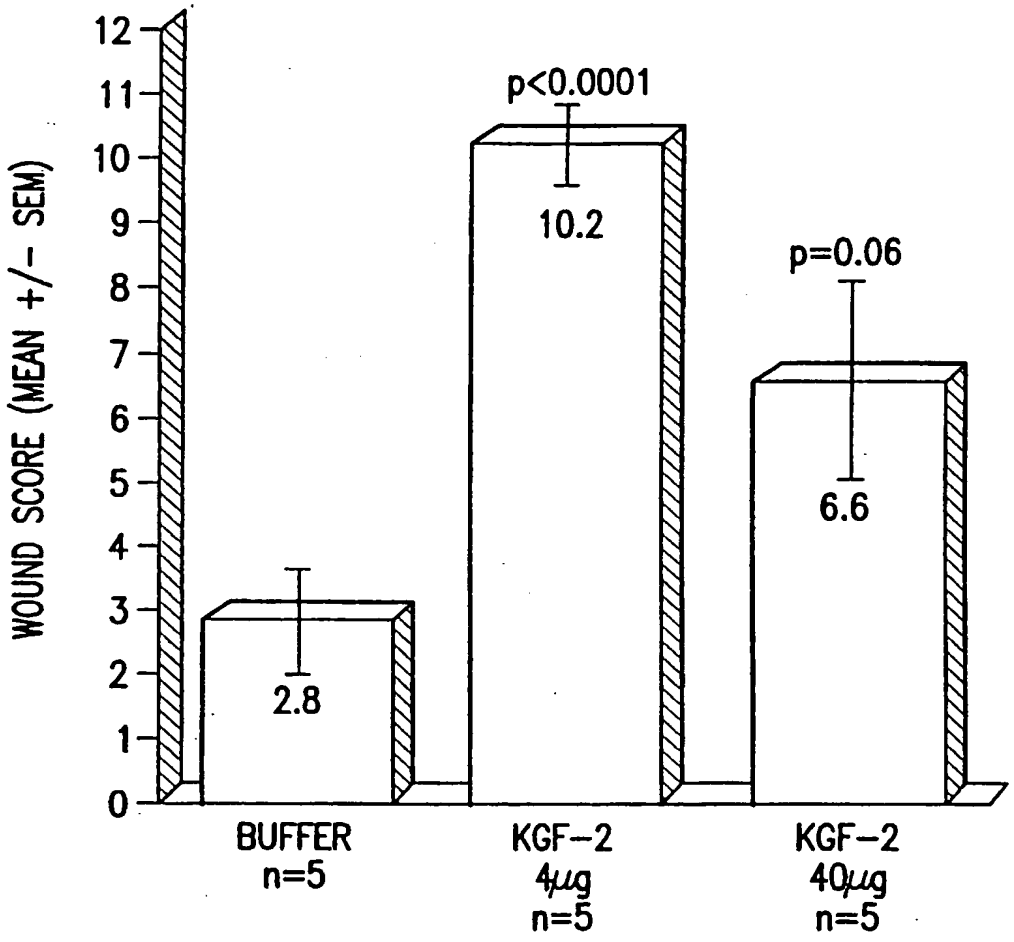
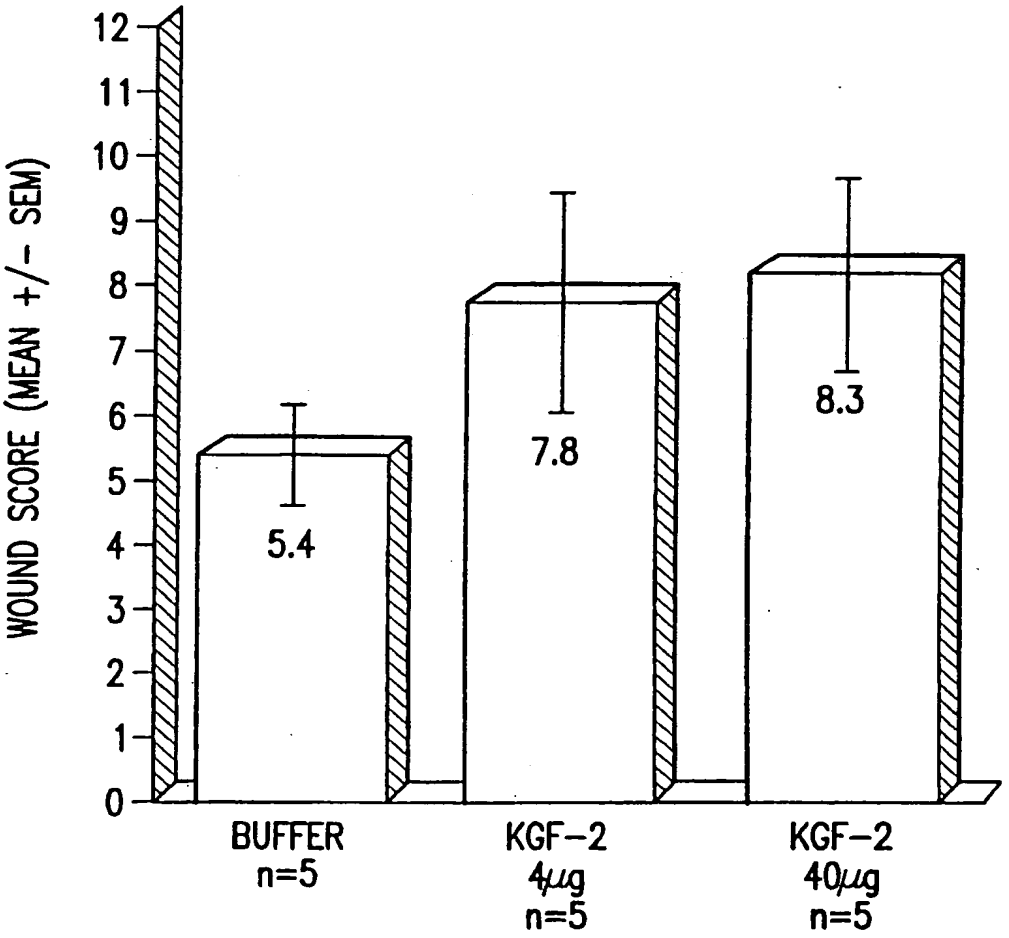

WOUND MEASURE AREA (sq. mm)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
1
2
3
4
5
8
DAYS POSTWOUNDING
VEHICLE n=5
KGF-2 40μg n=5
KGF-2 4μg n=5
p=0.02
p=0.03
p=0.04
p=0.004
p=0.01
p=0.02
p=0.02
p=0.002

FIG.8



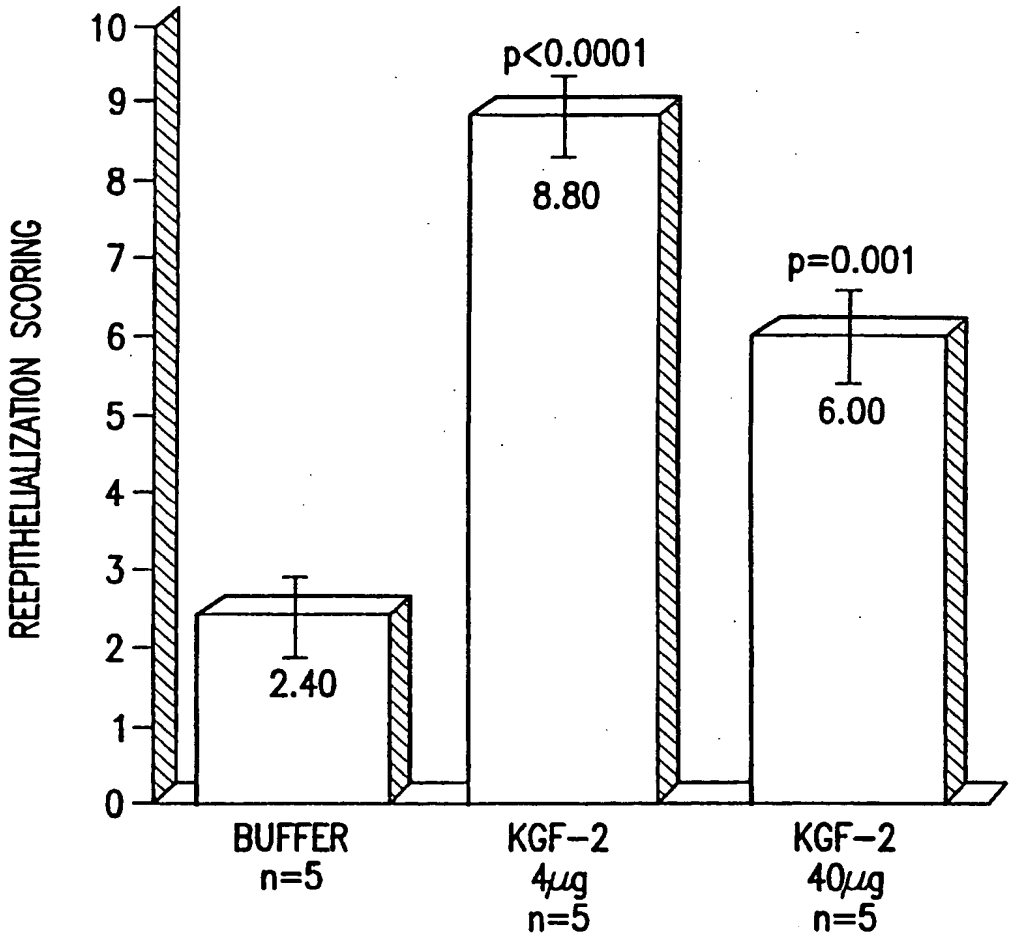
1-3 MINIMAL CELL ACCUMULATION, NO GRANULATION
4-6 IMMATURE GRANULATION, INFLAMMATORY CELLS, CAPILLARIES
10-12 FIBROBLASTS, COLLAGEN, EPITHELIUM

FIG.9



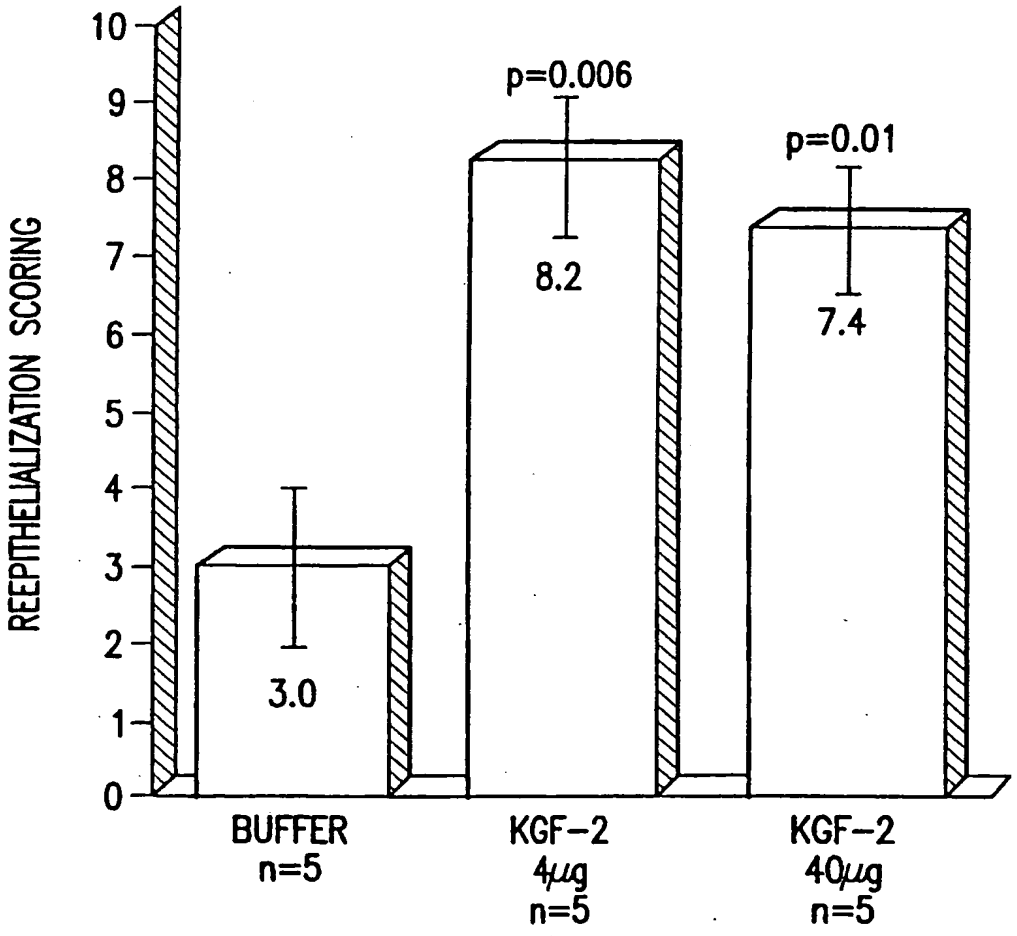
1-3 MINIMAL CELL ACCUMULATION, NO GRANULATION
4-6 IMMATURE GRANULATION, INFLAMMATORY CELLS, CAPILLARIES
7-9 GRANULATION TISSUE, CELLS, FIBROBLASTS, NEW EPITHELIUM
10-12 FIBROBLASTS, COLLAGEN, EPITHELIUM

FIG.10



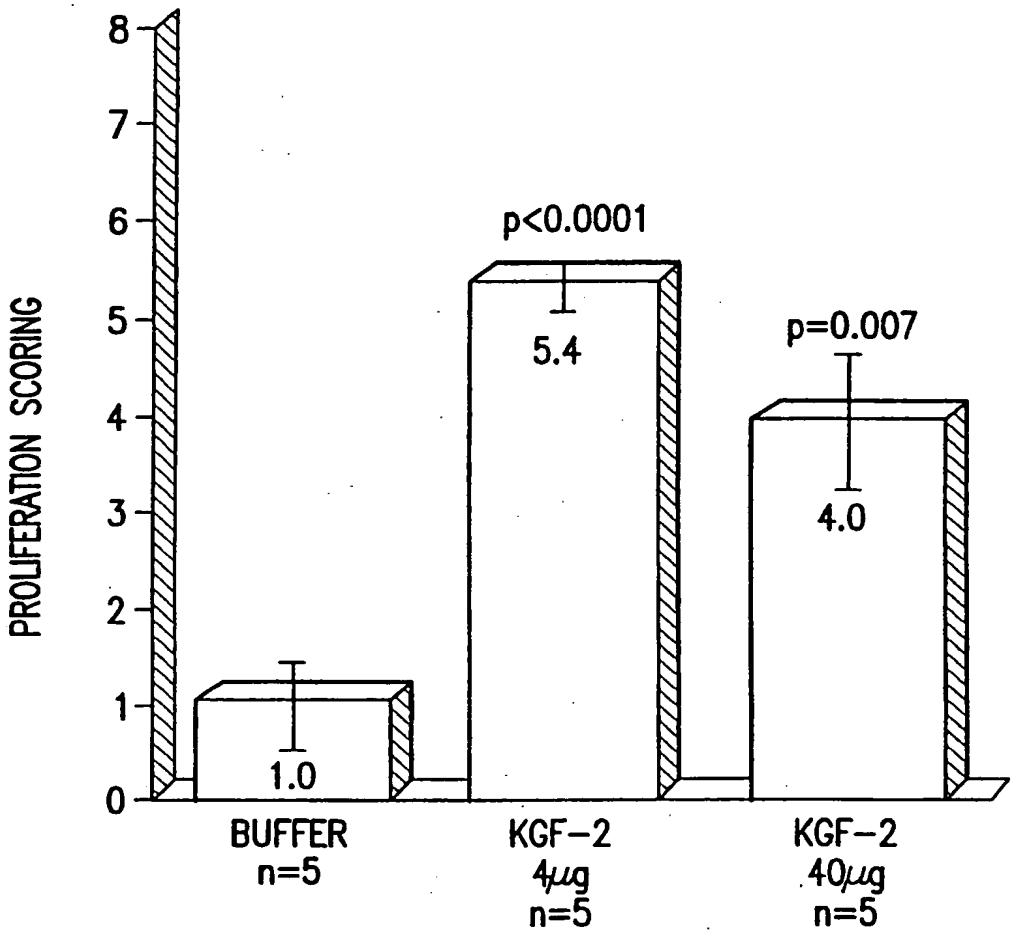
ANTI-CYTOKERATIN IMMUNOSTAINING
0-NO CLOSURE
5-SLIGHT TO MODERATE CLOSURE
10-COMPLETE CLOSURE

FIG.11



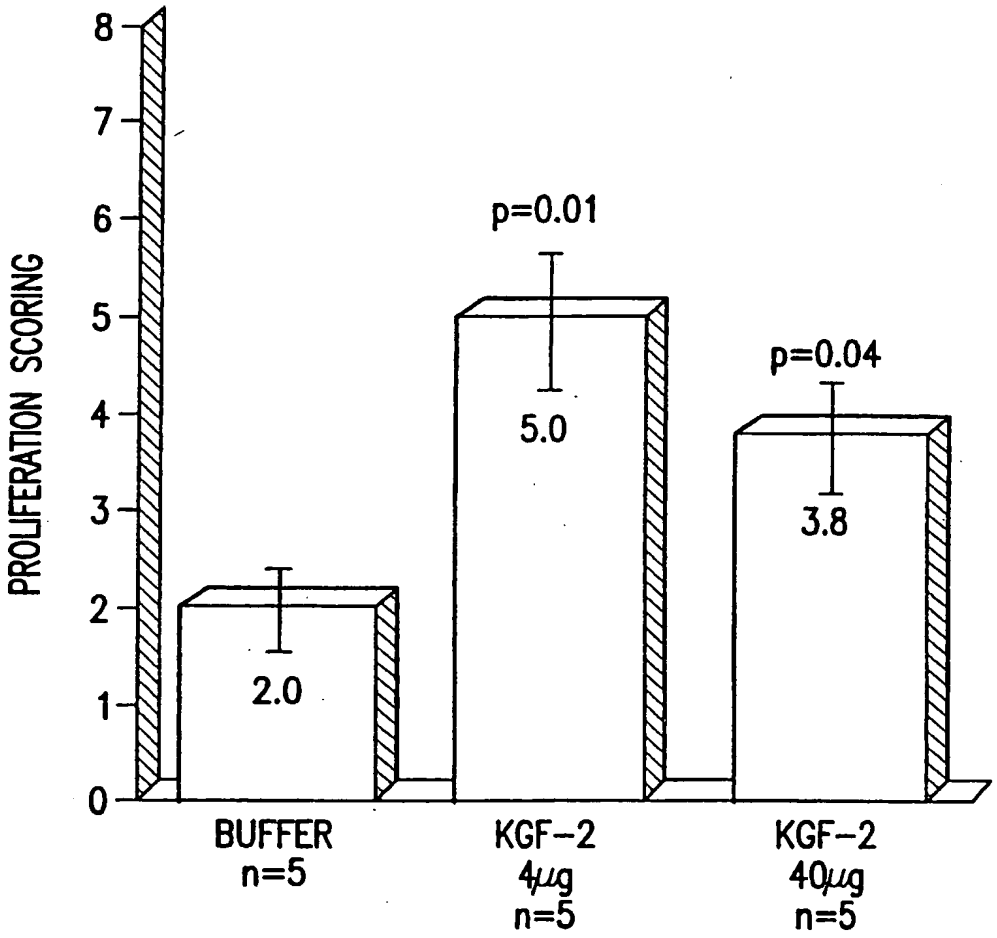
ANTI-CYTOKERATIN IMMUNOSTAINING
0-NO CLOSURE
5-SLIGHT TO MODERATE CLOSURE
10-COMPLETE CLOSURE

FIG.12



PCNA SCORING
0-2 SLIGHT PROLIFERATION
3-5 MODERATE PROLIFERATION
6-8 INTENSE PROLIFERATION

FIG.13



PCNA SCORING
0–2 SLIGHT PROLIFERATION
3–5 MODERATE PROLIFERATION
6–8 INTENSE PROLIFERATION

FIG.14

ATGAGAGGATCGCATCACCATCACCATCACGGATCCTGCCAGGCTCTGGGTC
AGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCTTCCTCTTTCTCTTCCC
CGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGTGACGTTC
GTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAA
AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTG
GAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAG
CAACTATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAG
AATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGAT
ACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTAT
GTGGCATTGAaTGGAAAAGGAGCTCCAaGGAGAGGACAGAAAACACGAAG
GAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MRGSHHHHHHGSCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGD
VRWRKLFSFTKYFLKIEKNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSN
YYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVA
LNGKGAPRRGQKTRRKNTSAHFLPMVVHS

kgf-2 synthetic cys37 Bam HI
AAAGGATCCTGCCAGGCTCTGGGTCAGGACATG

FIG.15

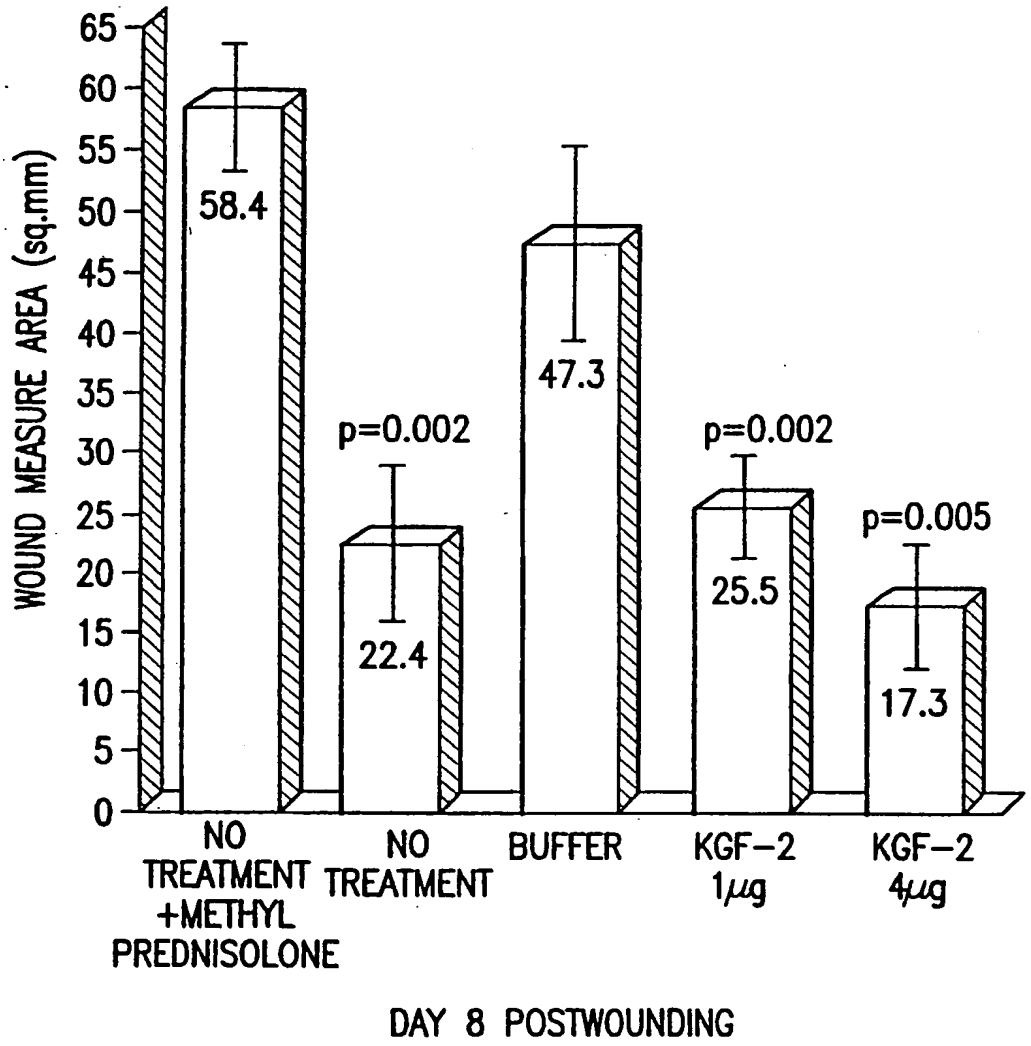

WOUND MEASURE AREA (sq.mm)
65
60
55
50
45
40
35
30
25
20
15
10
5
0
58.4
p=0.002
22.4
47.3
p=0.002
25.5
p=0.005
17.3
NO TREATMENT +METHYL PREDNISOLONE
NO TREATMENT
BUFFER
KGF-2 1μg
KGF-2 4μg
DAY 8 POSTWOUNDING

FIG.16

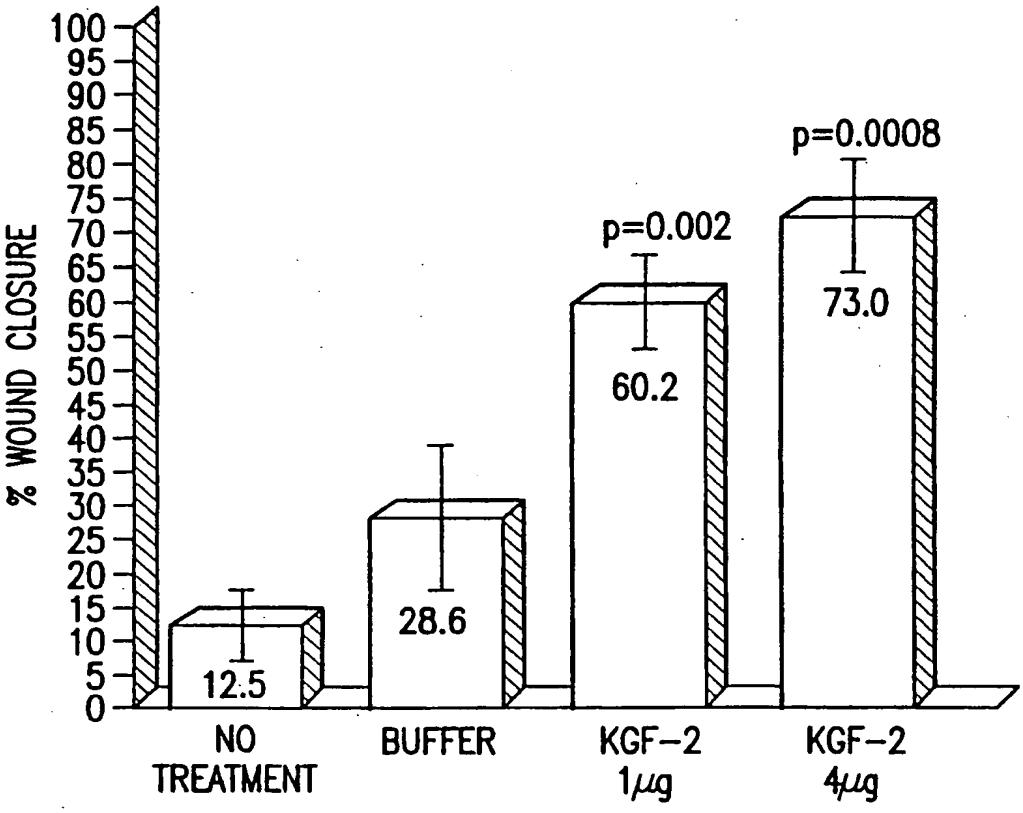

% WOUND CLOSURE
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
12.5
28.6
60.2
73.0
p=0.002
p=0.0008
NO TREATMENT
BUFFER
KGF-2 1μg
KGF-2 4μg
GLUCOCORTICOID TREATED ANIMALS

FIG.17

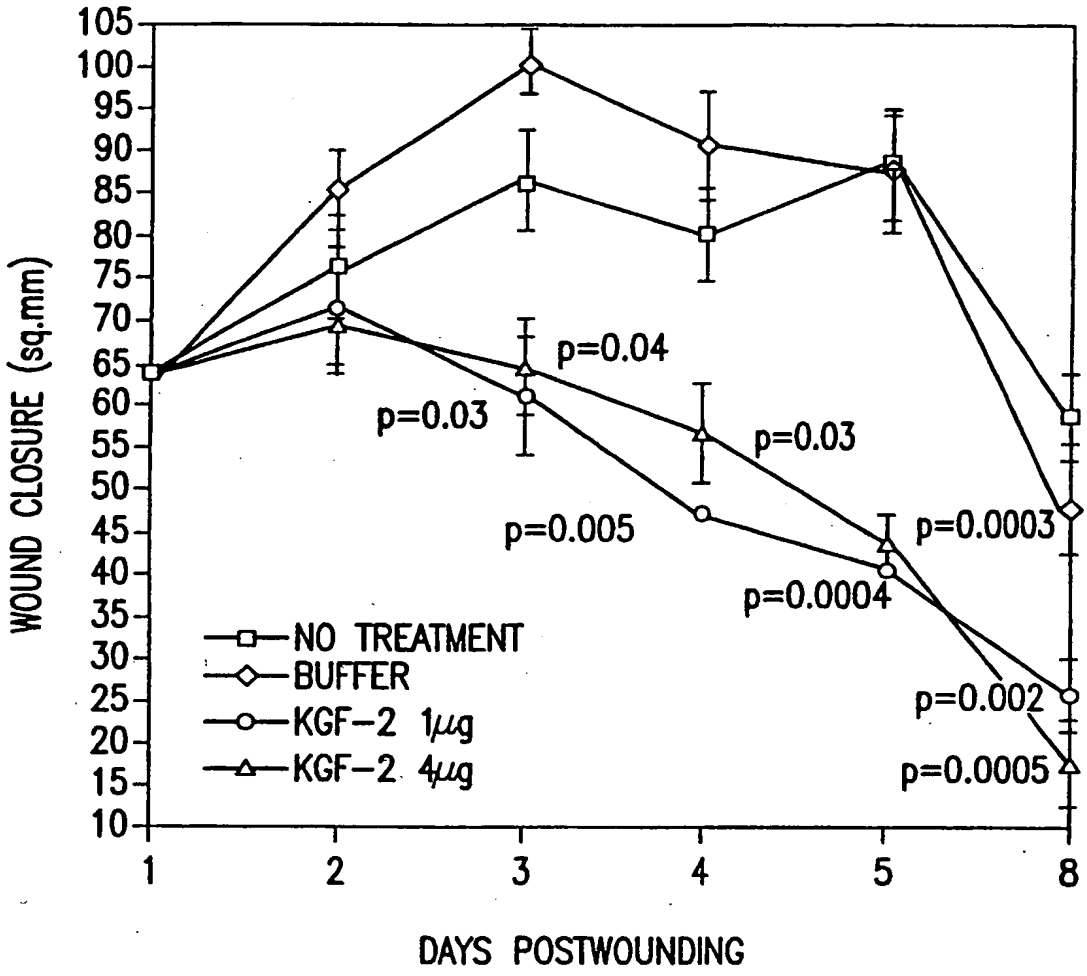

WOUND CLOSURE (sq.mm)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
1
2
3
4
5
8
DAYS POSTWOUNDING
NO TREATMENT
BUFFER
KGF-2 1μg
KGF-2 4μg
p=0.04
p=0.03
p=0.03
p=0.005
p=0.0003
p=0.0004
p=0.002
p=0.0005

FIG.18

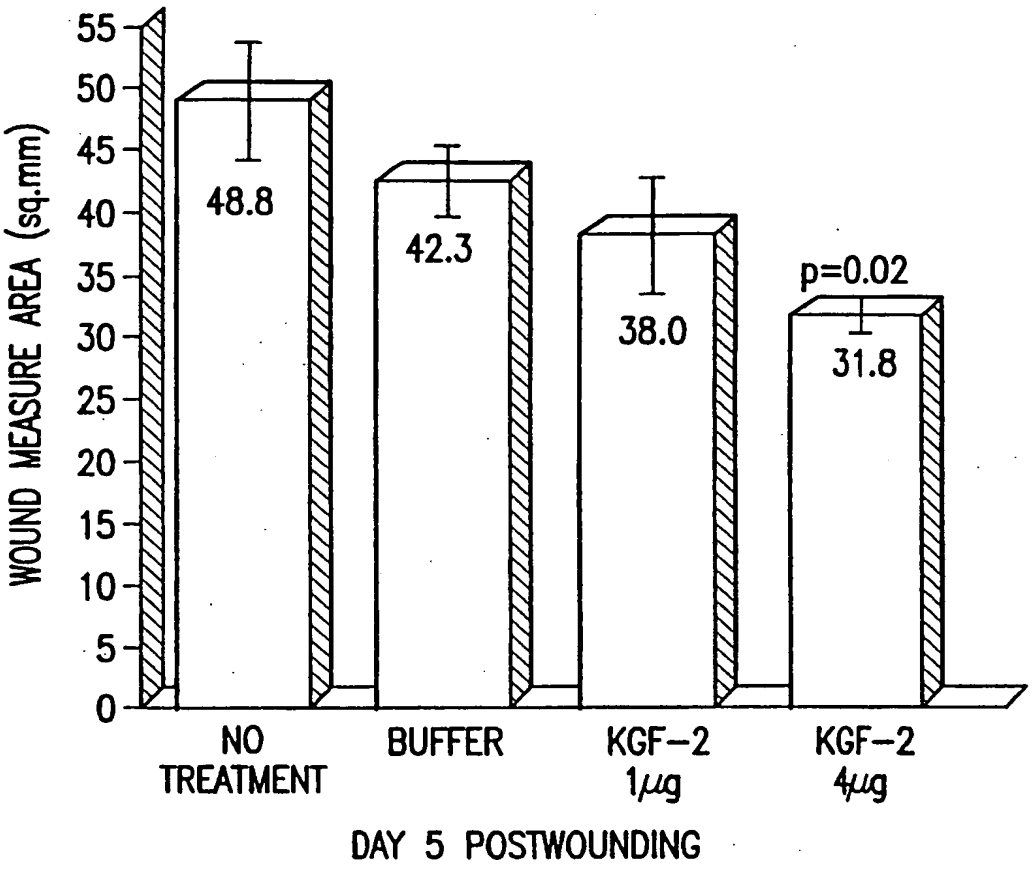

WOUND MEASURE AREA (sq.mm)
55
50
45
40
35
30
25
20
15
10
5
0
48.8
42.3
38.0
p=0.02
31.8
NO TREATMENT
BUFFER
KGF-2 1μg
KGF-2 4μg
DAY 5 POSTWOUNDING

FIG.19A

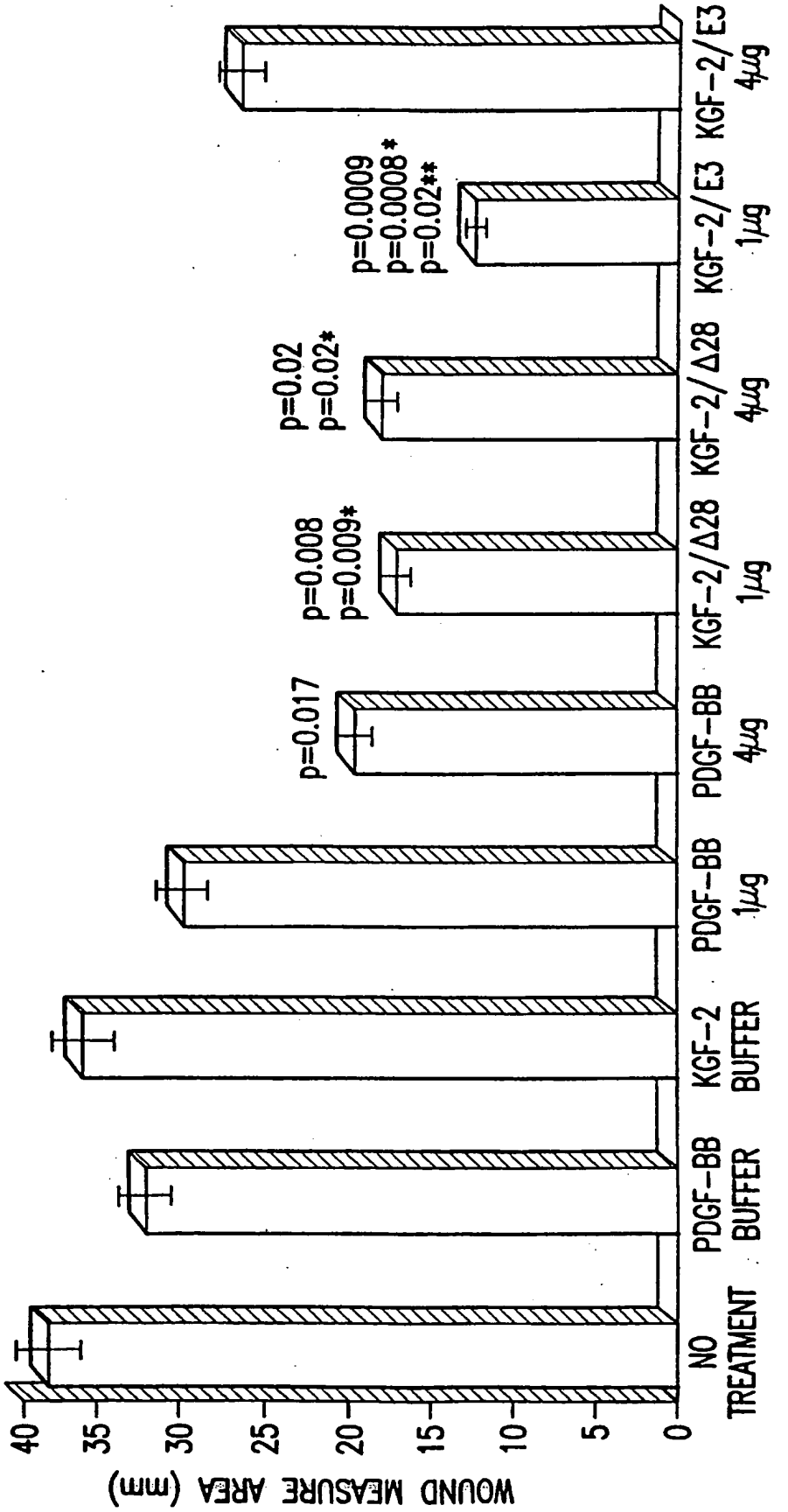

WOUND MEASURE AREA (mm)
0
5
10
15
20
25
30
35
40
NO TREATMENT
PDGF-BB BUFFER
KGF-2 BUFFER
PDGF-BB 1μg
PDGF-BB 4μg
KGF-2/Δ28 1μg
KGF-2/Δ28 4μg
KGF-2/E3 1μg
KGF-2/E3 4μg
p=0.017
p=0.008
p=0.009*
p=0.02
p=0.02*
p=0.0009
p=0.0008*
p=0.02**
DAY 10 POSTWOUNDING

FIG.19B

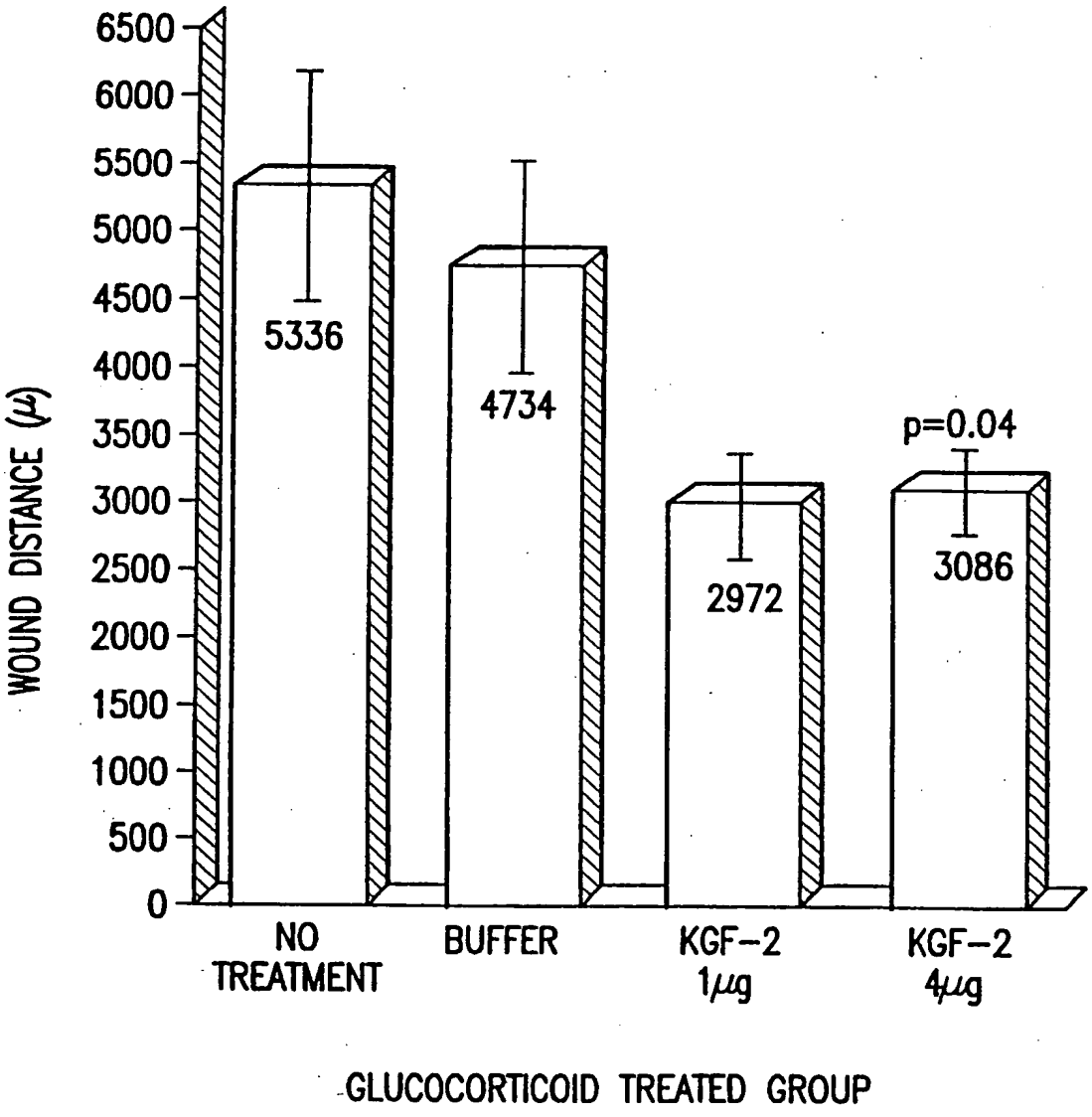

6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
WOUND DISTANCE (μ)
5336
4734
2972
p=0.04
3086
NO TREATMENT
BUFFER
KGF-2 1μg
KGF-2 4μg
GLUCOCORTICOID TREATED GROUP

FIG.20

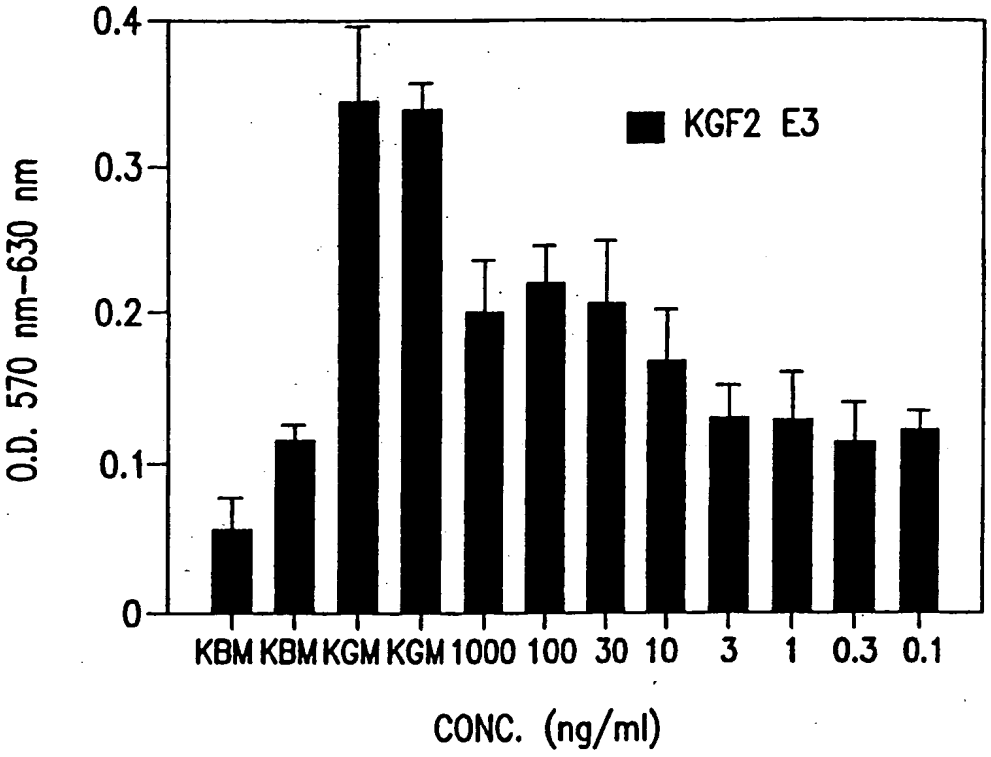


FIG.21A

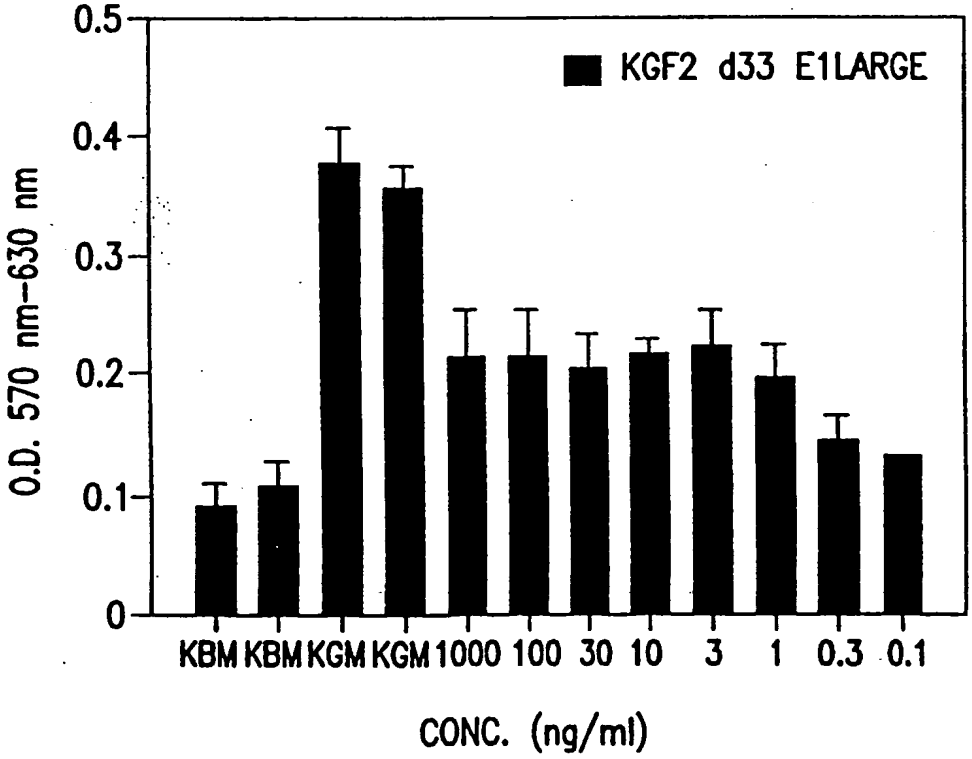


FIG.21B

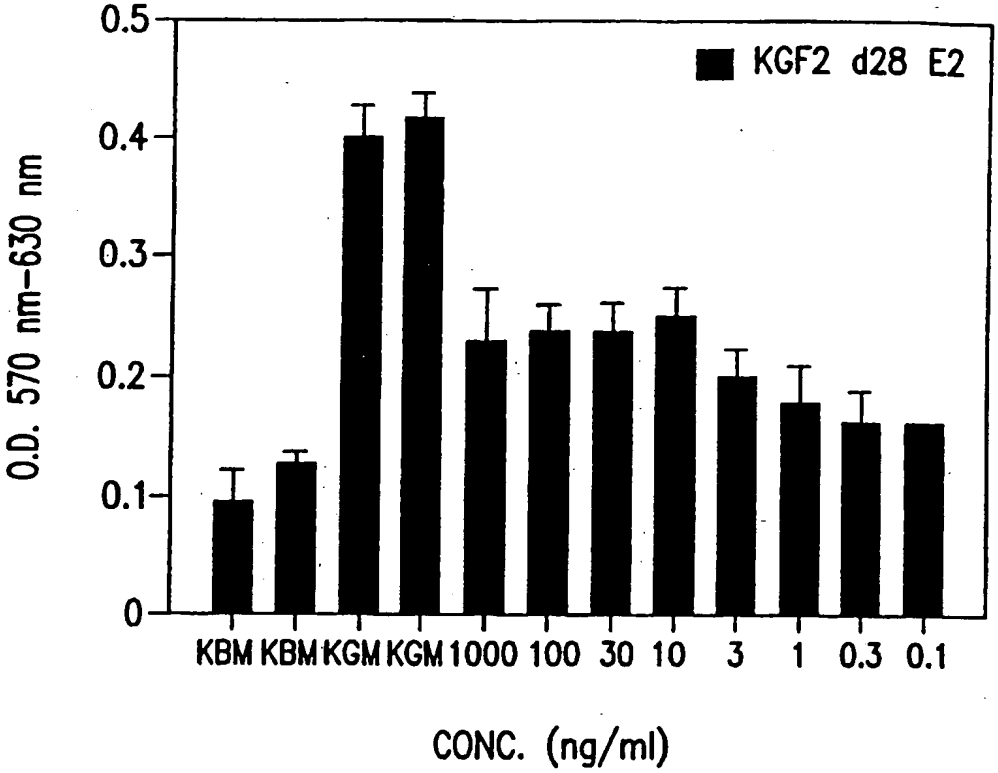


FIG.21C

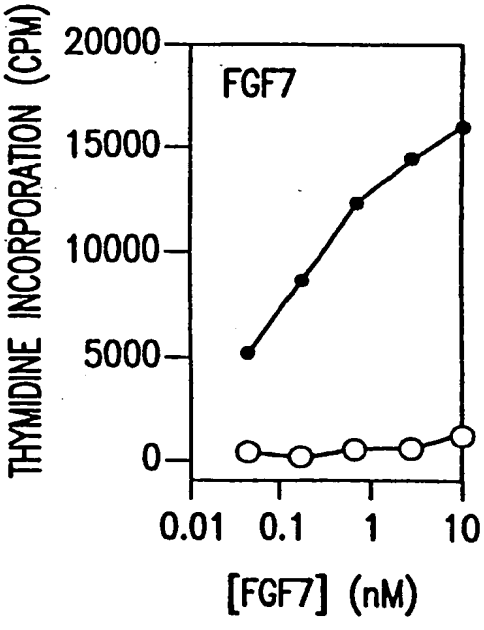


FIG.22A

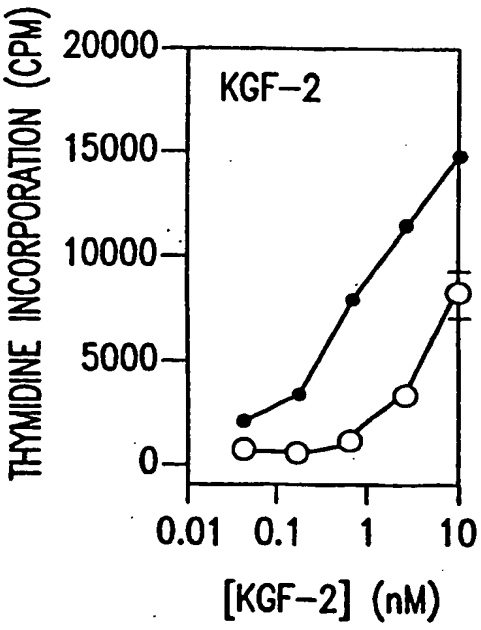


FIG.22A-1

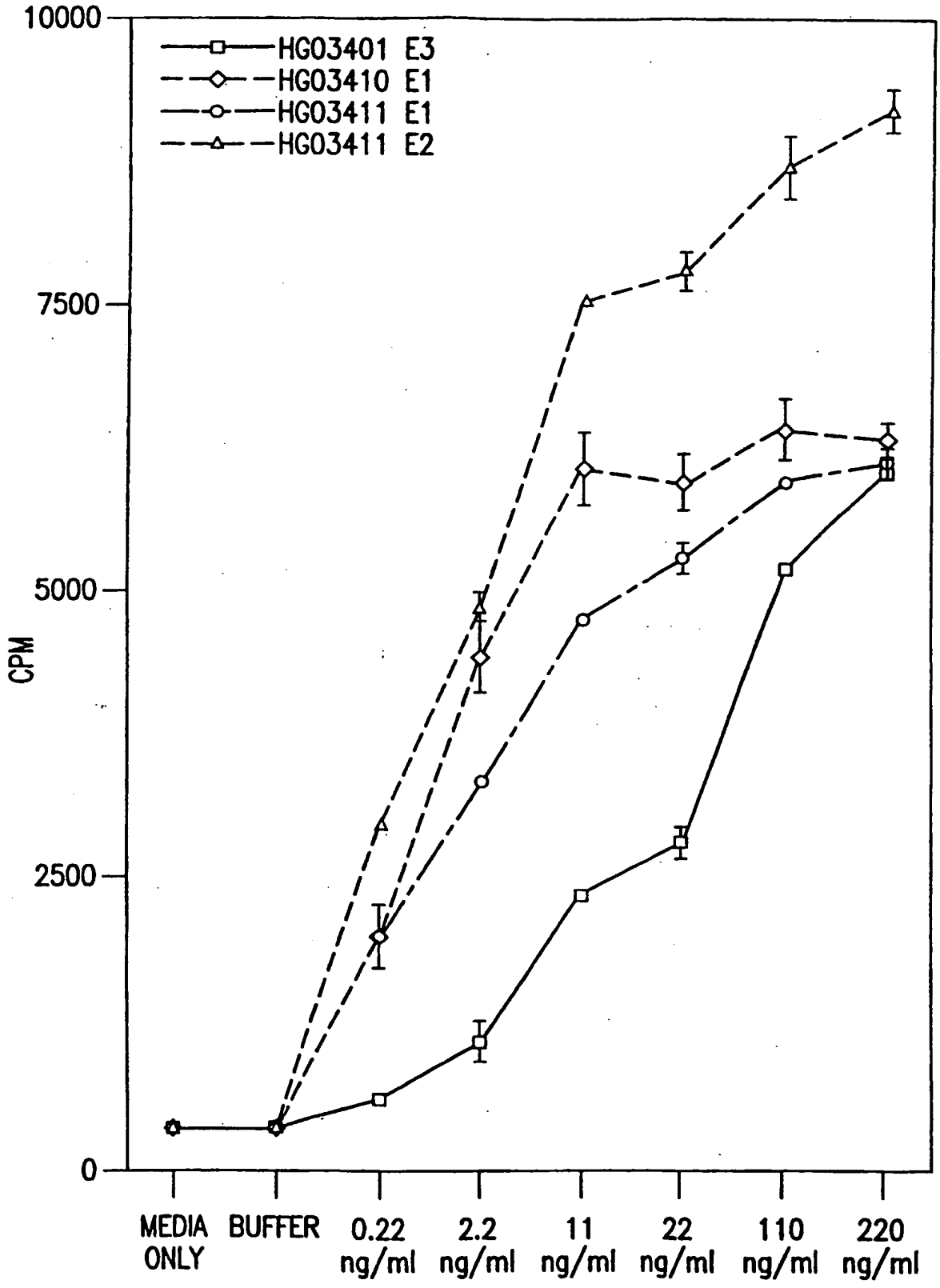

10000
7500
5000
2500
0
CPM
HG03401 E3
HG03410 E1
HG03411 E1
HG03411 E2
MEDIA ONLY
BUFFER
0.22 ng/ml
2.2 ng/ml
11 ng/ml
22 ng/ml
110 ng/ml
220 ng/ml

FIG.22B

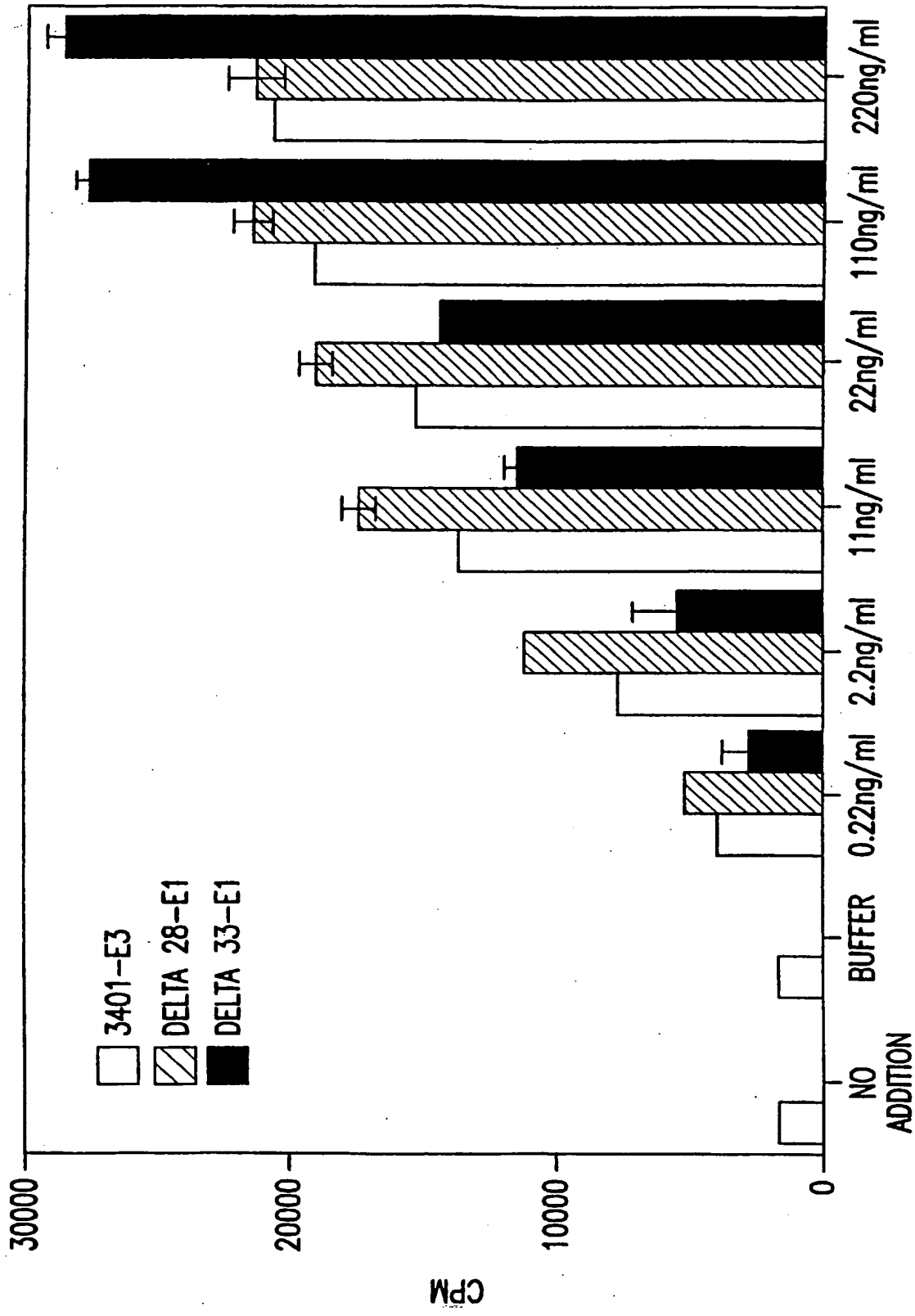

CPM
30000
20000
10000
0
3401-E3
DELTA 28-E1
DELTA 33-E1
NO ADDITION
BUFFER
0.22ng/ml
2.2ng/ml
11ng/ml
22ng/ml
110ng/ml
220ng/ml

FIG.22C

ATGTGGAAATGGATACTGACCCACTGCGCTTCTGCTTTCCCGCACCTGCCGGGTTGCTGC 60
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro Gly Cys Cys

TGCTGCTGCTTCCTGCTGCTGTTCCTGGTTTCTTCTGTTCCGGTTACCTGCCAGGCTCTG 120
Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val Pro Val Thr Cys Gln Ala Leu

GGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCTTCCTCTTTCTCTTCCCCG 180
Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro

ACTTCCGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGTGACGTTCGTTGGCGT 240
Thr Ser Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg

AAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAAAACGGTAAAGTTTCTGGG 300
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly

ACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTT 360
Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val

GTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAACTC 420
Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu

TATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGA 480
Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly

TACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTG 540
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu

AATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCAC 600
Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His

TTTCTTCCAATGGTGGTACACTCATAG 627
Phe Leu Pro Met Val Val His Ser *

FIG.23

```
ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCT   60
MetThrCysGlnAlaLeuGlyGlnAspMetValSerProGluAlaThrAsnSerSerSer

TCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAG  120
SerSerPheSerSerProSerSerAlaGlyArgHisValArgSerTyrAsnHisLeuGln

GGTGACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAA  180
GlyAspValArgTrpArgLysLeuPheSerPheThrLysTyrPheLeuLysIleGluLys

AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACA  240
AsnGlyLysValSerGlyThrLysLysGluAsnCysProTyrSerIleLeuGluIleThr

TCAGTAGAAATGGGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATG  300
SerValGluIleGlyValValAlaValLysAlaIleAsnSerAsnTyrTyrLeuAlaMet

AACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAG  360
AsnLysLysGlyLysLeuTyrGlySerLysGluPheAsnAsnAspCysLysLeuLysGlu

AGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGG  420
ArgIleGluGluAsnGlyTyrAsnThrTyrAlaSerPheAsnTrpGlnHisAsnGlyArg

CAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGG  480
GlnMetTyrValAlaLeuAsnGlyLysGlyAlaProArgArgGlyGlnLysThrArgArg

AAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG  525
LysAsnThrSerAlaHisPheLeuProMetValValHisSer *
```

FIG.24A

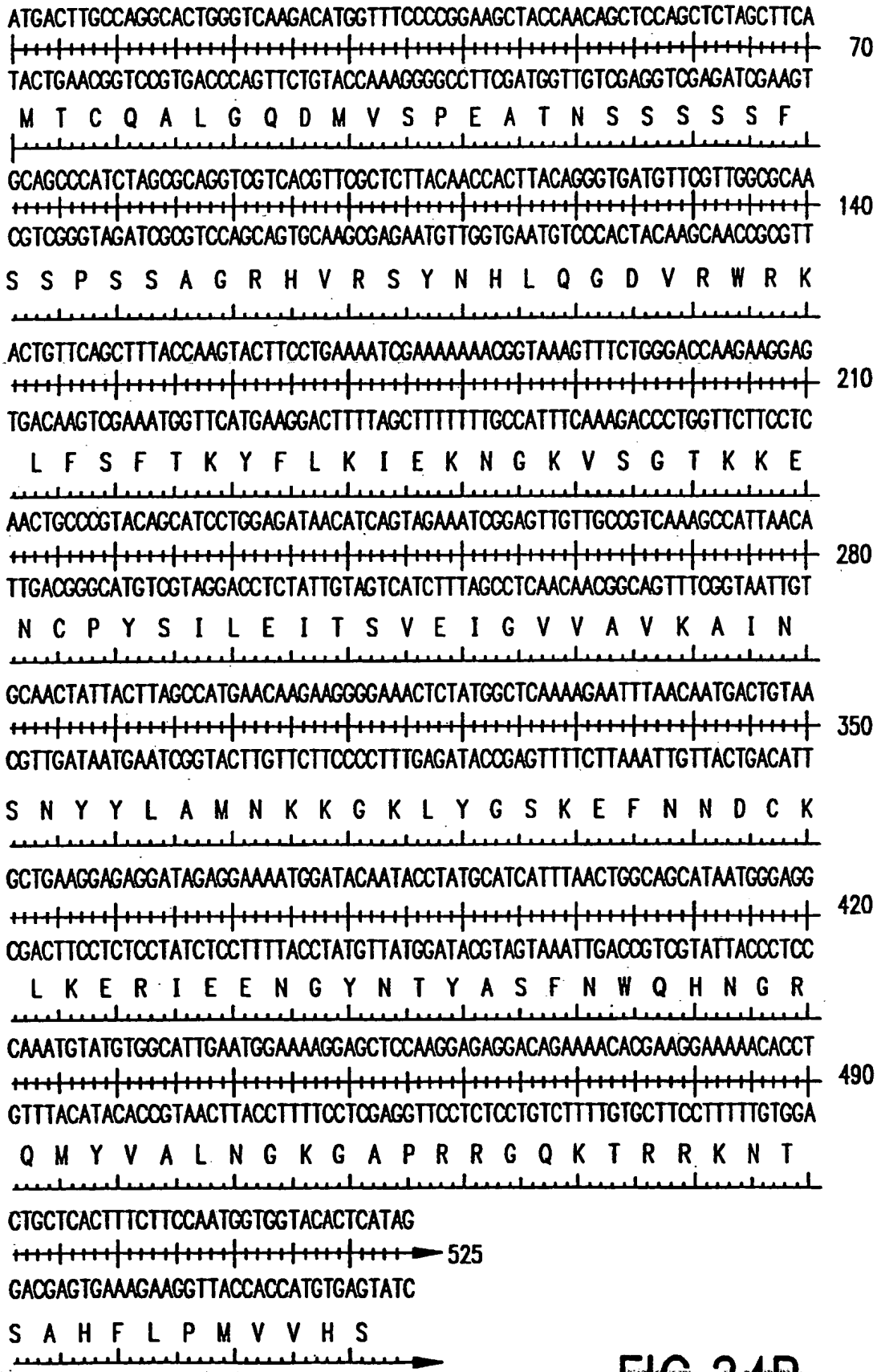

ATGACTTGCCAGGCACTGGGTCAAGACATGGTTTCCCCGGAAGCTACCAACAGCTCCAGCTCTAGCTTCA
70
TACTGAACGGTCCGTGACCCAGTTCTGTACCAAAGGGGCCTTCGATGGTTGTCGAGGTCGAGATCGAAGT
M T C Q A L G Q D M V S P E A T N S S S S S F
GCAGCCCATCTAGCGCAGGTCGTCACGTTCGCTCTTACAACCACTTACAGGGTGATGTTCGTTGGCGCAA
140
CGTCGGGTAGATCGCGTCCAGCAGTGCAAGCGAGAATGTTGGTGAATGTCCCACTACAAGCAACCGCGTT
S S P S S A G R H V R S Y N H L Q G D V R W R K
ACTGTTCAGCTTTACCAAGTACTTCCTGAAAATCGAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAG
210
TGACAAGTCGAAATGGTTCATGAAGGACTTTTAGCTTTTTTTGCCATTTCAAAGACCCTGGTTCTTCCTC
L F S F T K Y F L K I E K N G K V S G T K K E
AACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACA
280
TTGACGGGCATGTCGTAGGACCTCTATTGTAGTCATCTTTAGCCTCAACAACGGCAGTTTCGGTAATTGT
N C P Y S I L E I T S V E I G V V A V K A I N
GCAACTATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAA
350
CGTTGATAATGAATCGGTACTTGTTCTTCCCCTTTGAGATACCGAGTTTTCTTAAATTGTTACTGACATT
S N Y Y L A M N K K G K L Y G S K E F N N D C K
GCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGG
420
CGACTTCCTCTCCTATCTCCTTTTACCTATGTTATGGATACGTAGTAAATTGACCGTCGTATTACCCTCC
L K E R I E E N G Y N T Y A S F N W Q H N G R
CAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCT
490
GTTTACATACACCGTAACTTACCTTTTCCTCGAGGTTCCTCTCCTGTCTTTTGTGCTTCCTTTTTGTGGA
Q M Y V A L N G K G A P R R G Q K T R R K N T
CTGCTCACTTTCTTCCAATGGTGGTACACTCATAG
525
GACGAGTGAAAGAAGGTTACCACCATGTGAGTATC
S A H F L P M V V H S

FIG.24B

ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

MTCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGDVRWRKLFSFTKYFLKIE
KNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNNDCKL
KERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.25

ATGGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGTGACGTTCGTTGGCGT
AAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAAAACGGTAAAGTTTCT
GGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATC
GGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAG
GGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATA
GAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAA
ATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGG
AAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MAGRHVRSYNHLQGDVRWRKLFSFTKYFLKIEKNGKVSGTKKENCPYSILEITSVEIGV
VAVKAINSNYYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVA
LNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.26

ATGGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAA
AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATA
ACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTA
GCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAG
CTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAG
CATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGA
CAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCA
TAG

MVRWRKLFSFTKYFLKIEKNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSNYYLAM
NKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTR
RKNTSAHFLPMVVHS.

FIG.27

ATGGAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCAT
CCTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCA
ACTATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAAC
AATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATC
ATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAG
CTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCA
ATGGTGGTACACTCATAG

MEKNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNNDC
KLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVH
S.

FIG.28

ATGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTTGT
TGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAAC
TCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAA
AATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTA
TGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAA
ACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MENCPYSILEITSVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNNDCKLKERIEENGY
NTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.29

ATGGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAACT
CTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAA
ATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTAT
GTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAA
CACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MVKAINSNYYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMY
VALNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.30

ATGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAG
GATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGA
GGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACA
CGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKT
RRKNTSAHFLPMVVHS.

FIG.31

ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAG

MTCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGDVRWRKLFSFTKYFLKIE
KNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNNDCKL
K

FIG.32

ATGGCTGGTCGTCACGTTCGTTCTTACAACCACCTGCAGGGTGACGTTCGTTGGCGT
AAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAAAAACGGTAAAGTTTCT
GGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATC
GGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAG
GGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAG

MAGRHVRSYNHLQGDVRWRKLFSFTKYFLKIEKNGKVSGTKKENCPYSILEITSVEIGV
VAVKAINSNYYLAMNKKGKLYGSKEFNNDCKLK

FIG.33

C-37 To Ser

ATGACCTCTCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

FIG.34

C-106 To Ser

ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTCGTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTCTCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

FIG.35

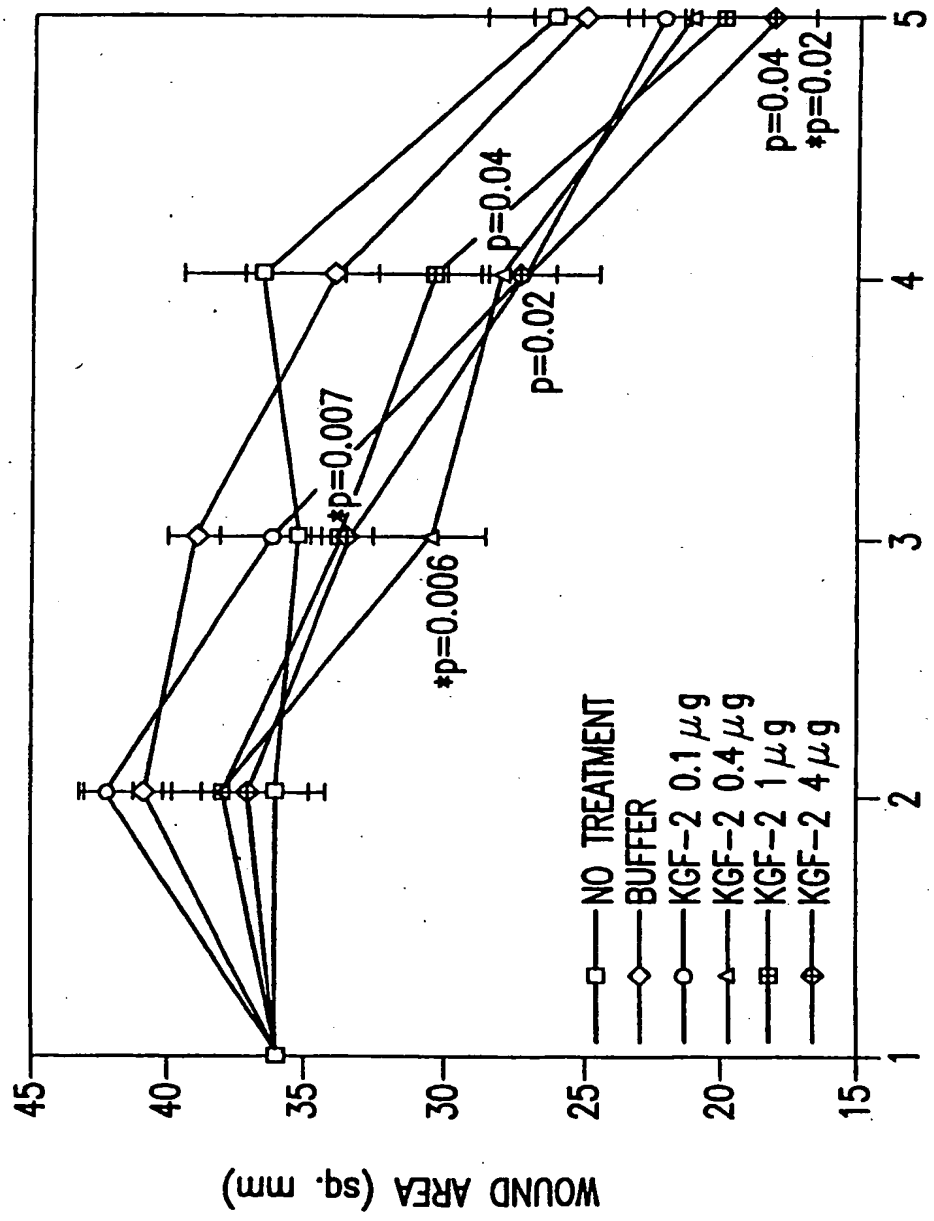

WOUND AREA (sq. mm)
45
40
35
30
25
20
15
1
2
3
4
5
DAYS POST-WOUNDING
NO TREATMENT
BUFFER
KGF-2 0.1 μg
KGF-2 0.4 μg
KGF-2 1 μg
KGF-2 4 μg
*p=0.006
*p=0.007
p=0.02
p=0.04
p=0.04
*p=0.02

FIG.36

EFFECT OF KGF-2 Δ33 ON NORMAL WOUND HEALING RAT MODEL

TREATMENT GROUPS	WOUND SIZE (mm)	% WOUND CLOSURE	HISTOLOGICAL SCORE	RE-EPITH. (μm)	BrdU SCORE
NO TREATMENT	25.9±2.5	58.8±3.7	6.8±0.2	1142±141	3.8±0.4
BUFFER	25.1±1.7	60.2±2.6	6.4±0.2	923±61	5.0±0.4
KGF-2/Δ33 (0.1μg)	22.0±0.9	65±1.4	6.8±0.2	1275±148	4.6±0.7
KGF-2/Δ33 (0.4μg)	21.1±1.4	68.4±2.4	8.0±0.5 p=0.0445*	1310±182	4.2±0.7
KGF-2/Δ33 (1.0μg)	19.9±1.5	66.2±2.1	8.4±0.4 p=0.0159* p=0.0053†	1389±115 p=0.0074†	3.3±0.25 p=0.0217†
KGF-2/Δ33 (4.0μg)	18.1±1.6 p=0.0398* p=0.0200†	71.2±2.6 p=0.0367* p=0.0217†	8.5±0.3 p=0.0047* p=0.0445†	1220±89 p=0.0254†	5.3±0.9

FIG.37

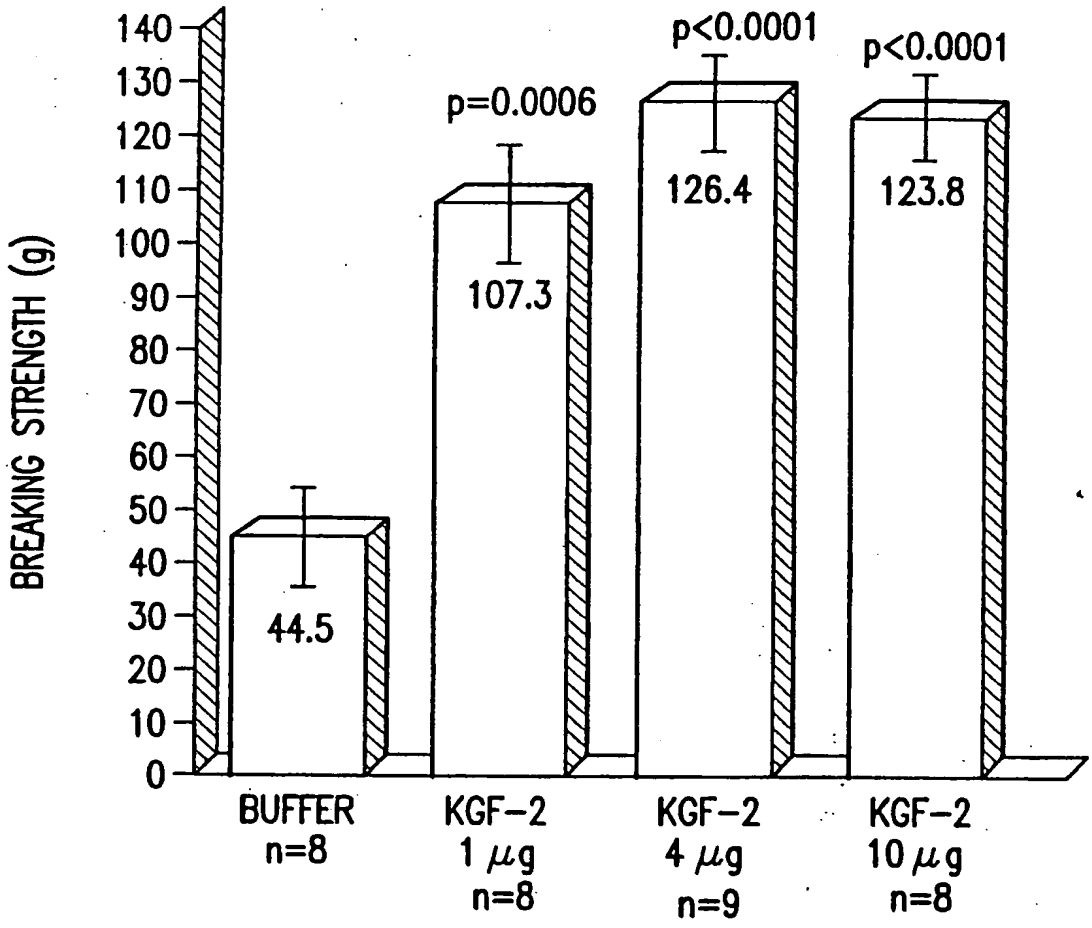

BREAKING STRENGTH (g)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
44.5
107.3
p=0.0006
126.4
p<0.0001
123.8
p<0.0001
BUFFER
n=8
KGF-2
1 μg
n=8
KGF-2
4 μg
n=9
KGF-2
10 μg
n=8

FIG.38

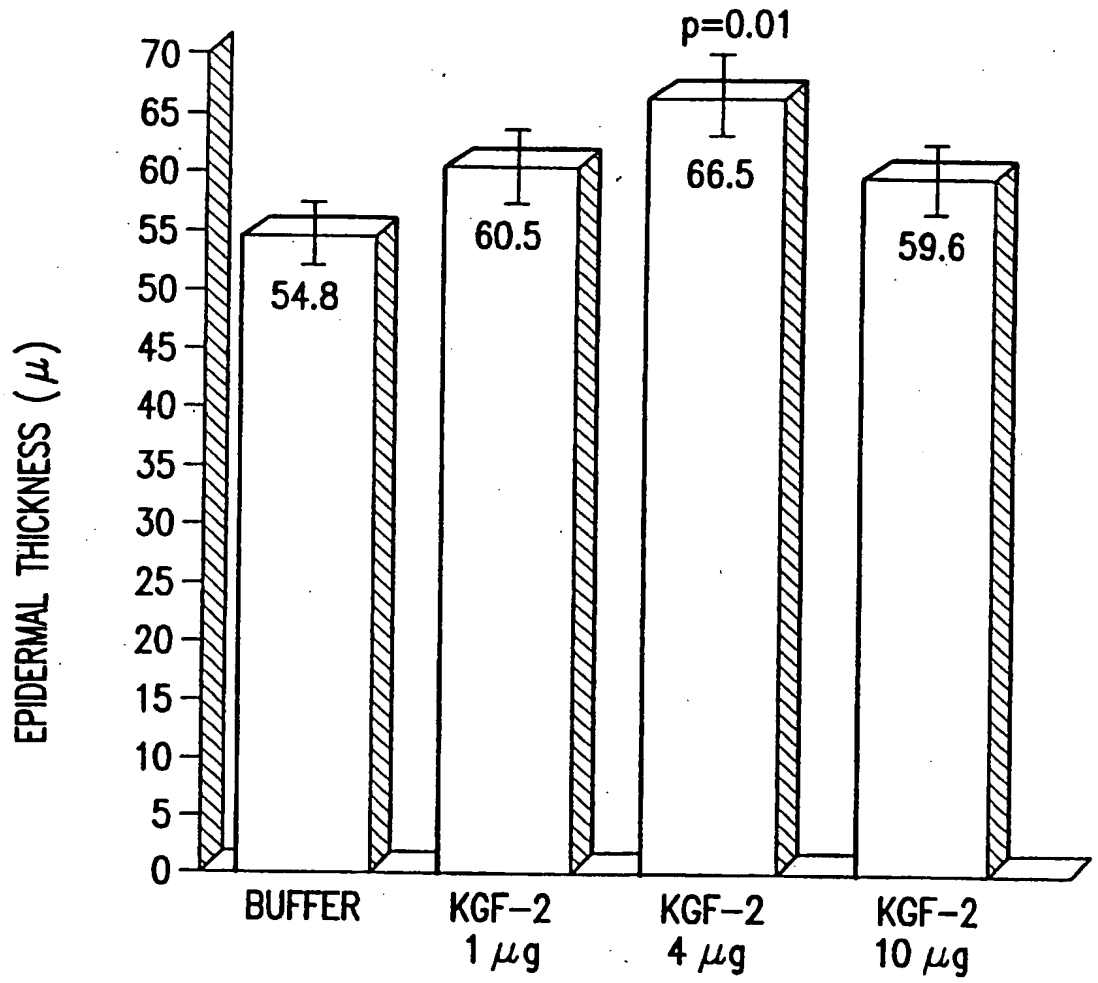

p=0.01
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
EPIDERMAL THICKNESS (μ)
54.8
60.5
66.5
59.6
BUFFER
KGF-2 1 μg
KGF-2 4 μg
KGF-2 10 μg

FIG.39

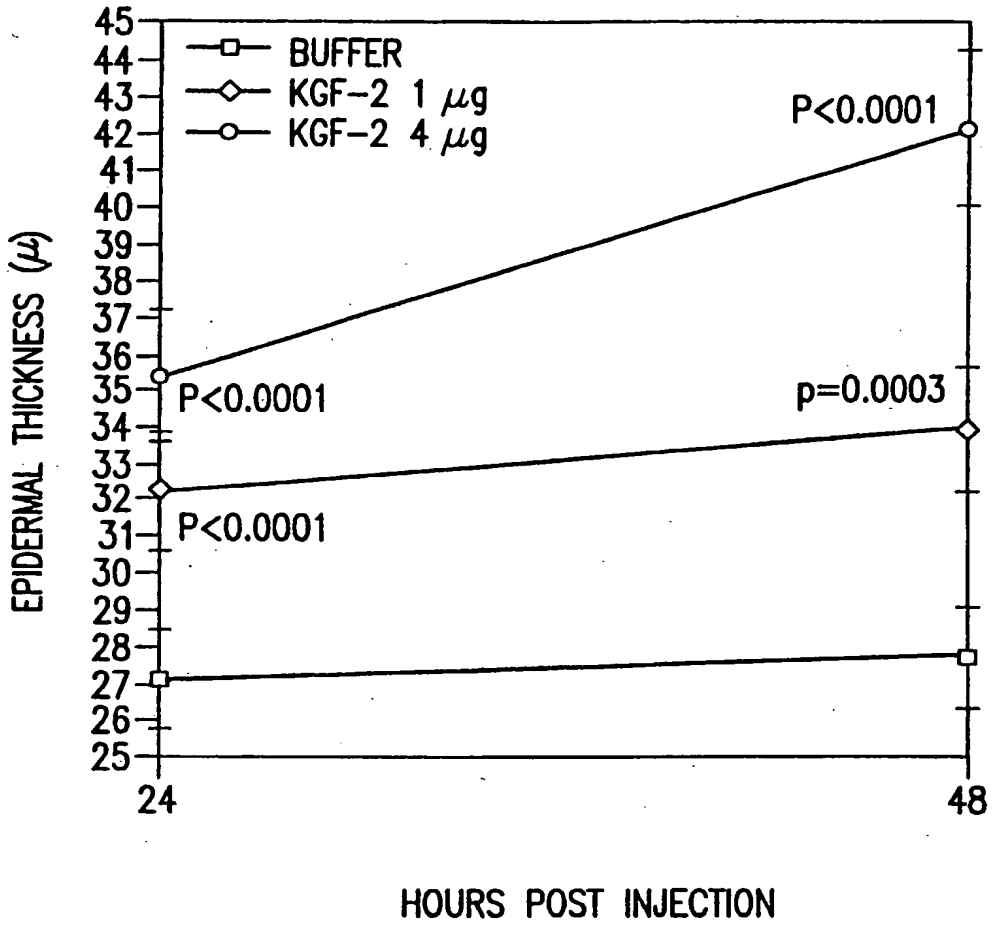

BUFFER
KGF-2 1 μg
KGF-2 4 μg
P<0.0001
P<0.0001
p=0.0003
P<0.0001
EPIDERMAL THICKNESS (μ)
45
44
43
42
41
40
39
38
37
36
35
34
33
32
31
30
29
28
27
26
25
24
48
HOURS POST INJECTION

FIG.40

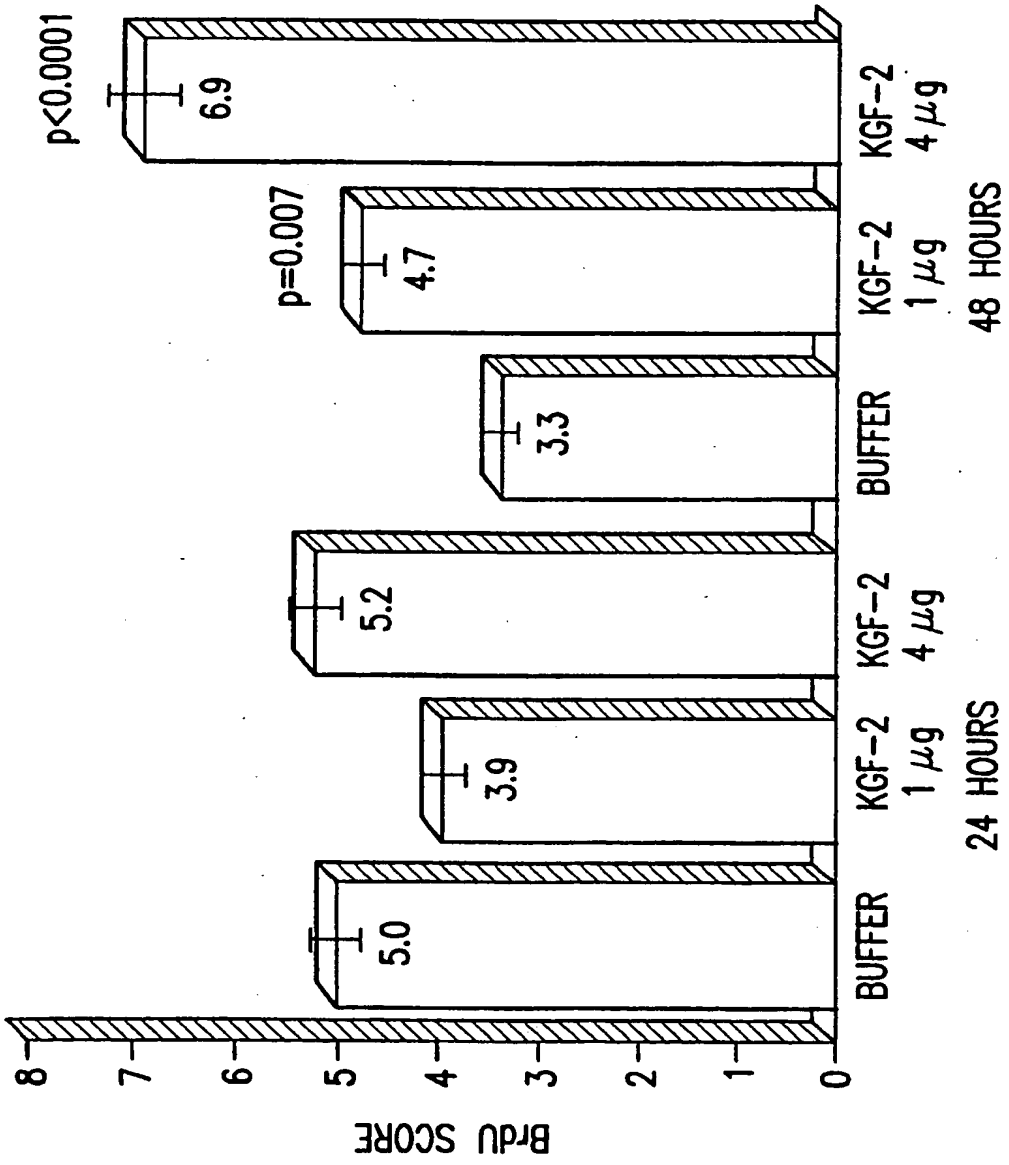

BrdU SCORE
0
1
2
3
4
5
6
7
8
5.0
3.9
5.2
3.3
4.7
6.9
p=0.007
p<0.0001
BUFFER
KGF-2 1 μg
KGF-2 4 μg
BUFFER
KGF-2 1 μg
KGF-2 4 μg
24 HOURS
48 HOURS

FIG.41

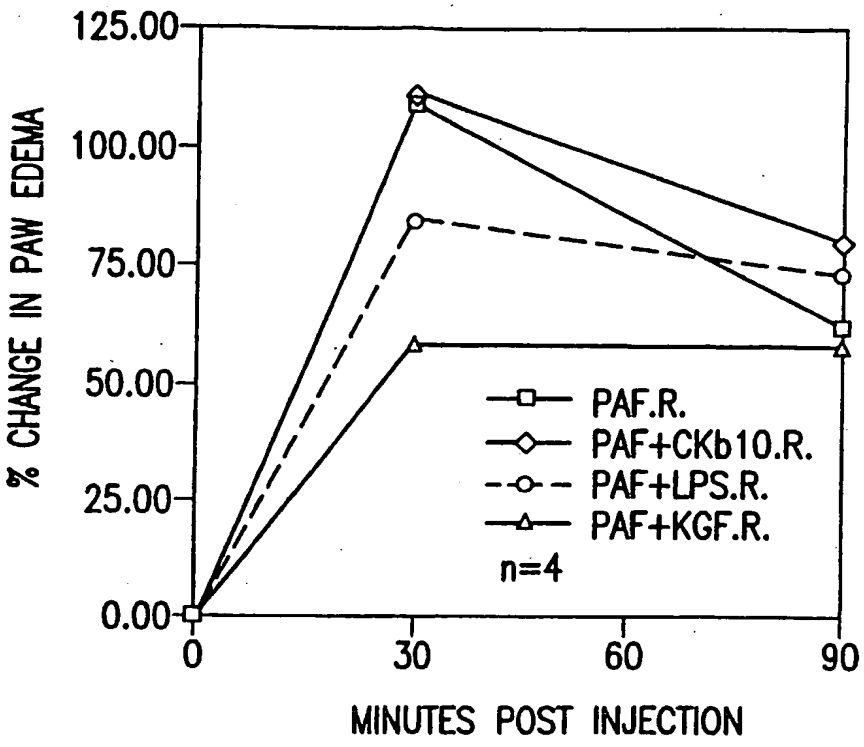


FIG.42A

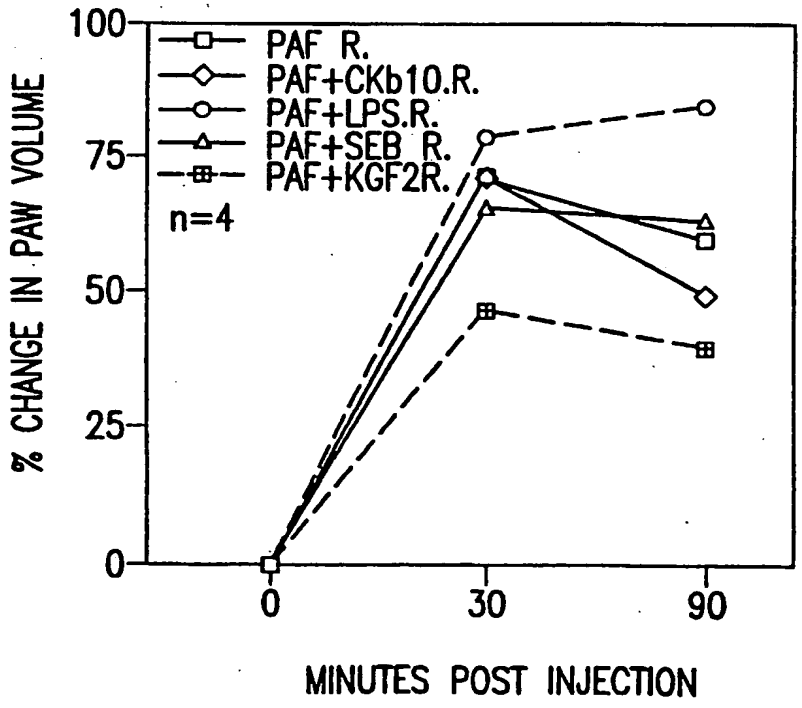


FIG.42B

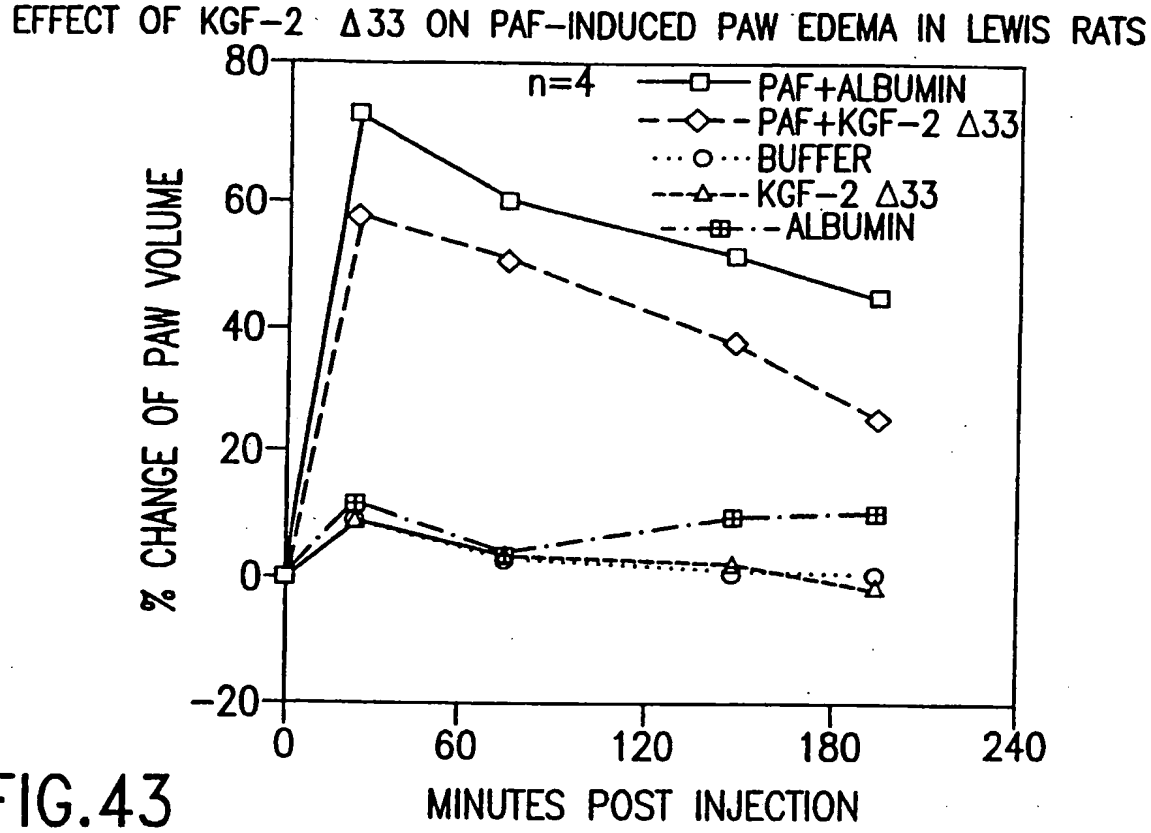

EFFECT OF KGF-2 Δ33 ON PAF-INDUCED PAW EDEMA IN LEWIS RATS
n=4
PAF+ALBUMIN
PAF+KGF-2 Δ33
BUFFER
KGF-2 Δ33
ALBUMIN
% CHANGE OF PAW VOLUME
80
60
40
20
0
-20
0
60
120
180
240
MINUTES POST INJECTION

FIG.43

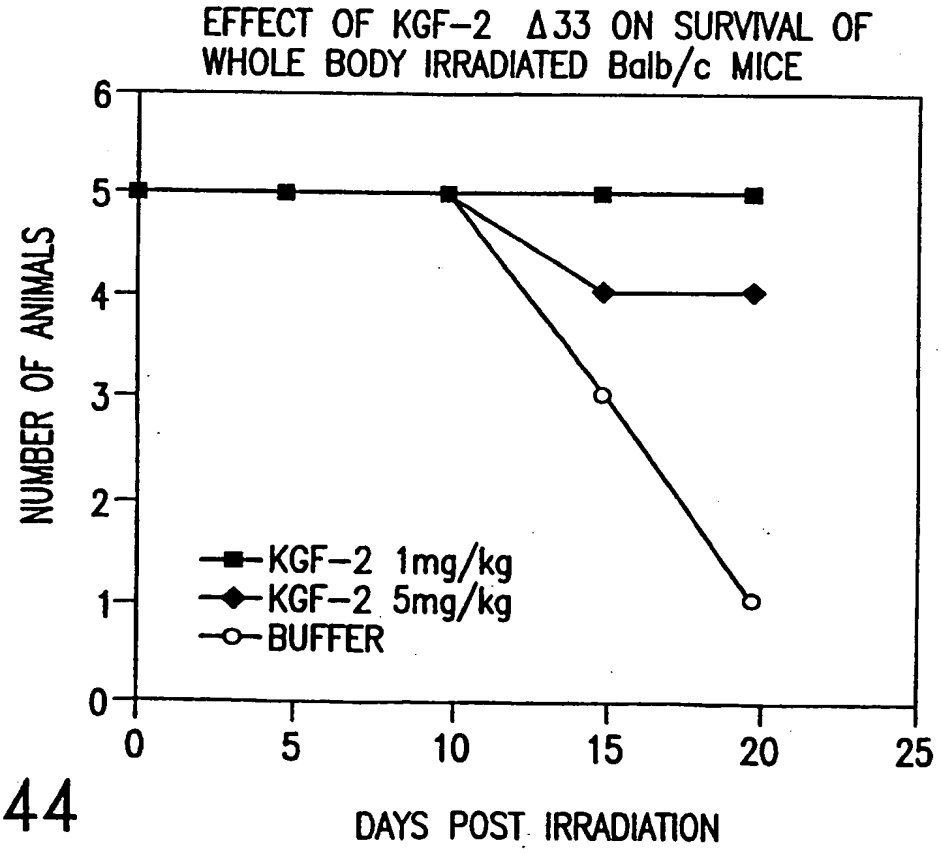

EFFECT OF KGF-2 Δ33 ON SURVIVAL OF WHOLE BODY IRRADIATED Balb/c MICE
NUMBER OF ANIMALS
6
5
4
3
2
1
0
KGF-2 1mg/kg
KGF-2 5mg/kg
BUFFER
0
5
10
15
20
25
DAYS POST IRRADIATION

FIG.44

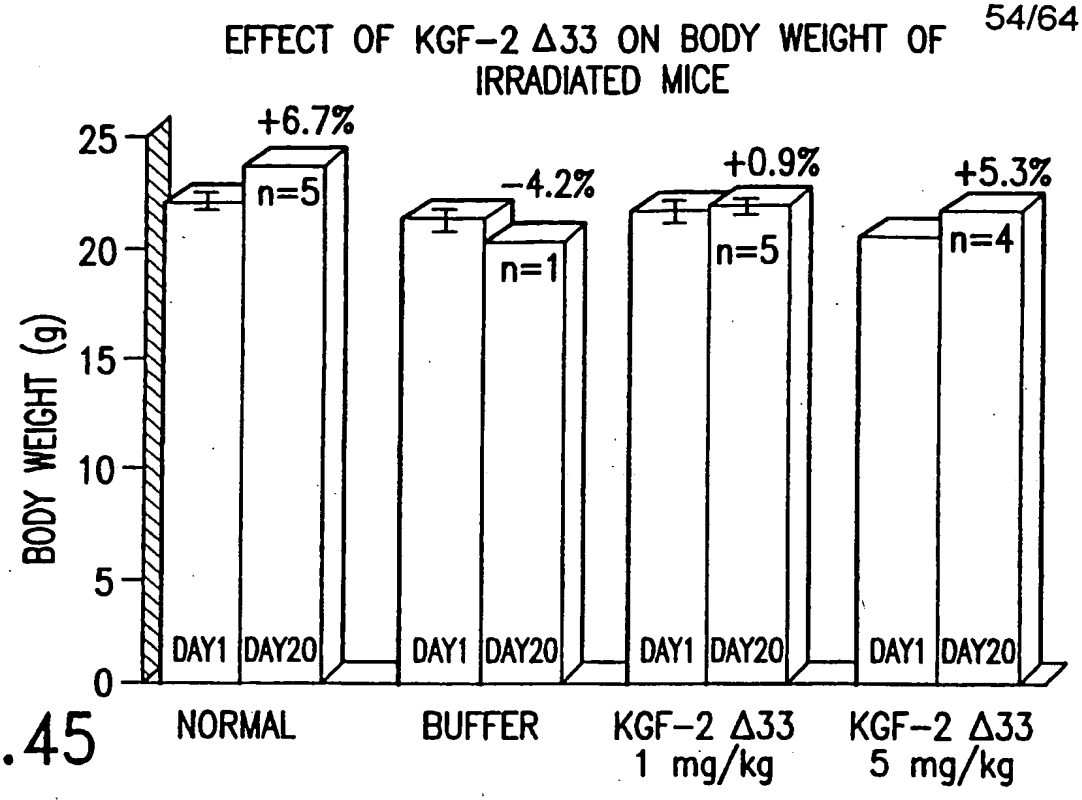

EFFECT OF KGF-2 Δ33 ON BODY WEIGHT OF IRRADIATED MICE
BODY WEIGHT (g)
25
20
15
10
5
0
+6.7%
n=5
-4.2%
n=1
+0.9%
n=5
+5.3%
n=4
DAY1
DAY20
NORMAL
BUFFER
KGF-2 Δ33 1 mg/kg
KGF-2 Δ33 5 mg/kg

FIG.45

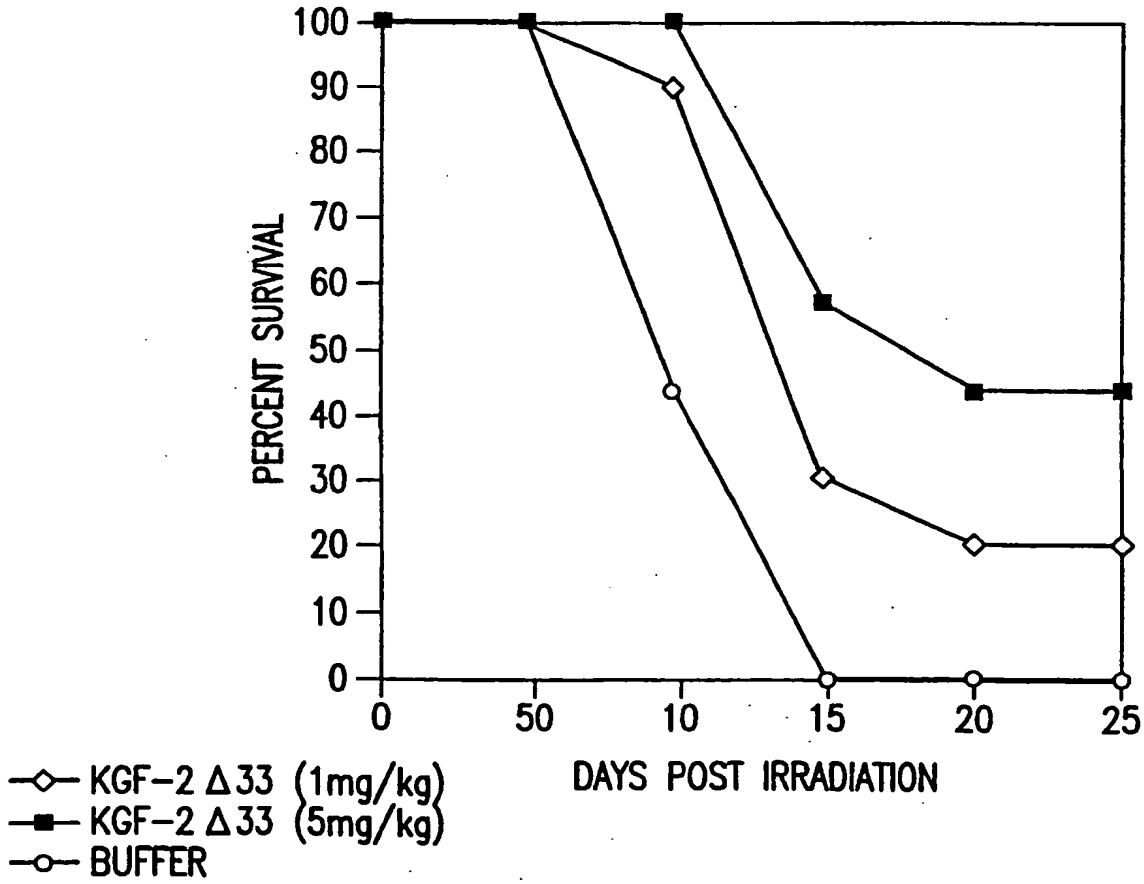

PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
50
10
15
20
25
DAYS POST IRRADIATION
KGF-2 Δ33 (1mg/kg)
KGF-2 Δ33 (5mg/kg)
BUFFER

FIG.46

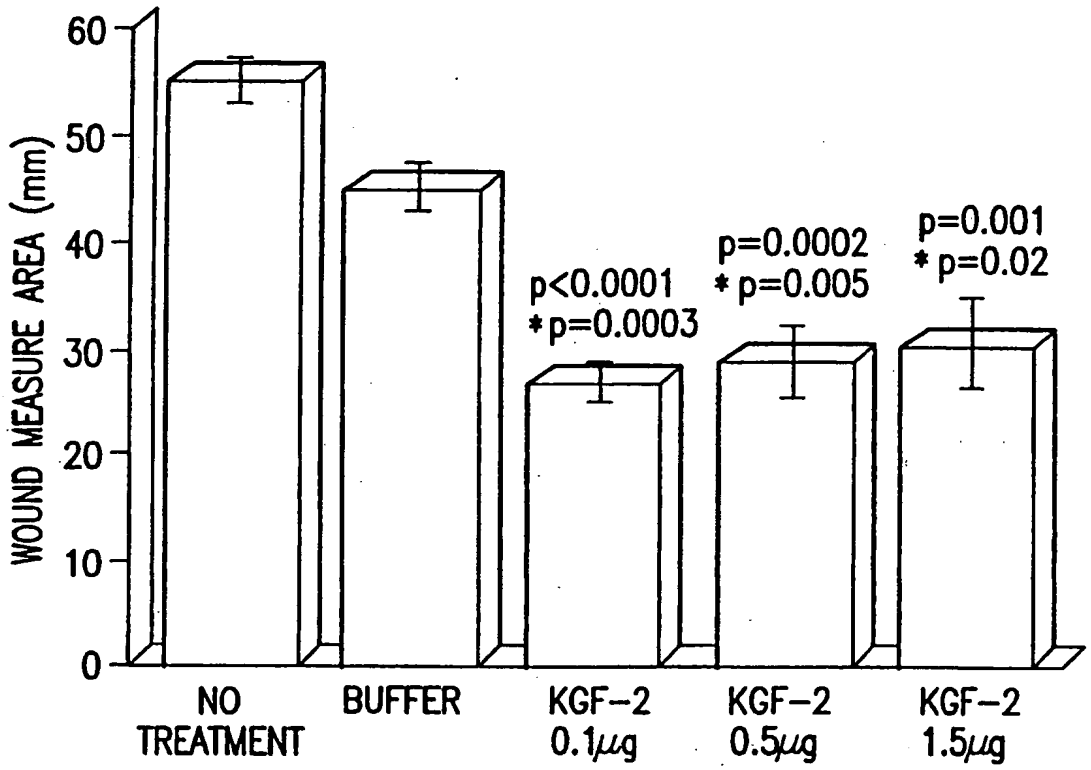

WOUND MEASURE AREA (mm)
60
50
40
30
20
10
0
p<0.0001
*p=0.0003
p=0.0002
*p=0.005
p=0.001
*p=0.02
NO TREATMENT
BUFFER
KGF-2 0.1μg
KGF-2 0.5μg
KGF-2 1.5μg
DAY 8 POSTWOUNDING

FIG.47

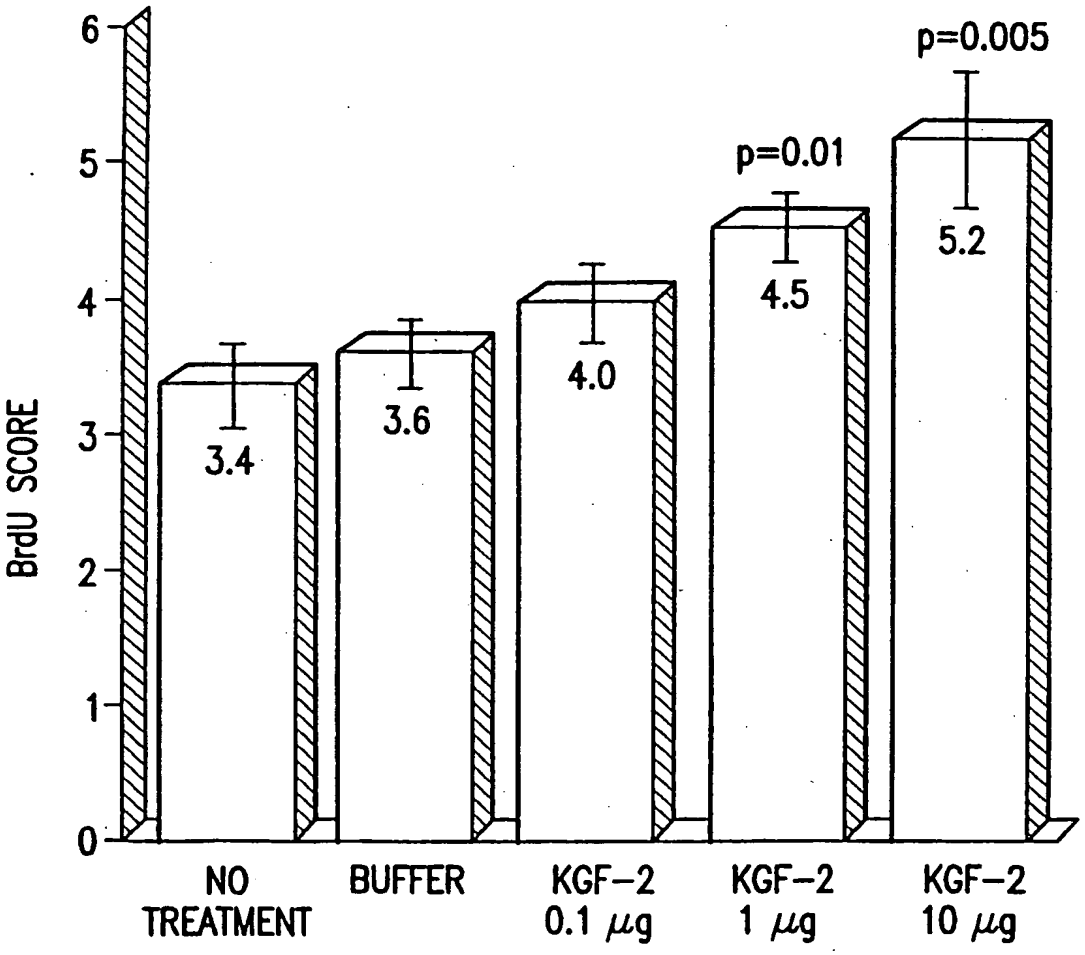

BrdU SCORE
0
1
2
3
4
5
6
3.4
3.6
4.0
4.5
5.2
p=0.01
p=0.005
NO TREATMENT
BUFFER
KGF-2 0.1 μg
KGF-2 1 μg
KGF-2 10 μg

FIG.48

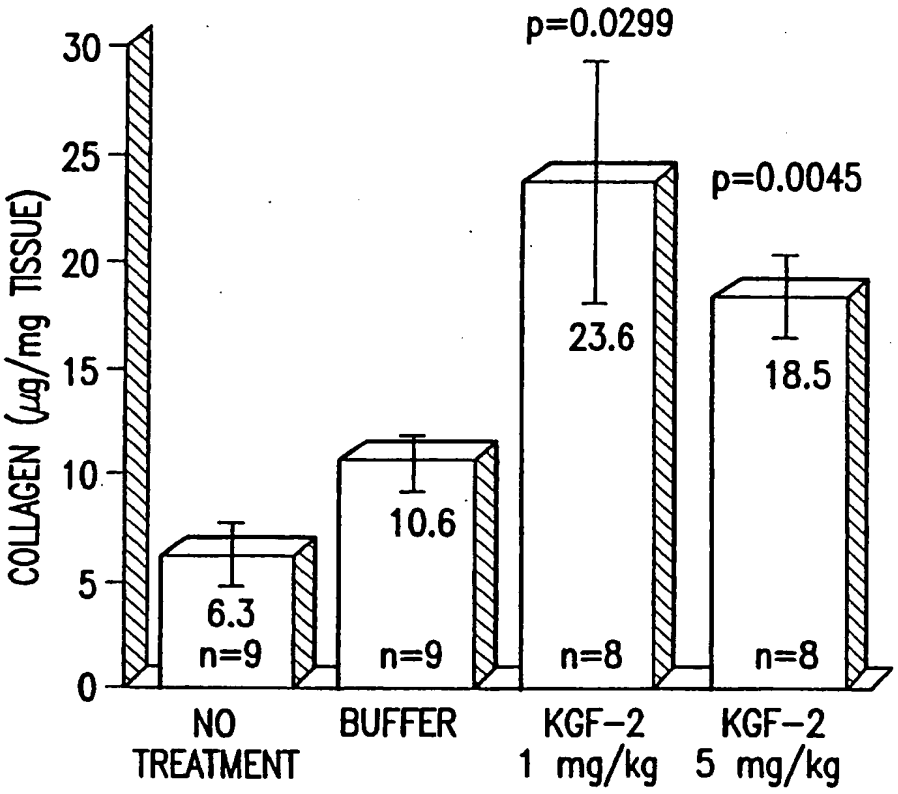

p=0.0299
p=0.0045
30
25
20
15
10
5
0
COLLAGEN (μg/mg TISSUE)
6.3
n=9
10.6
n=9
23.6
n=8
18.5
n=8
NO TREATMENT
BUFFER
KGF-2 1 mg/kg
KGF-2 5 mg/kg

FIG.49

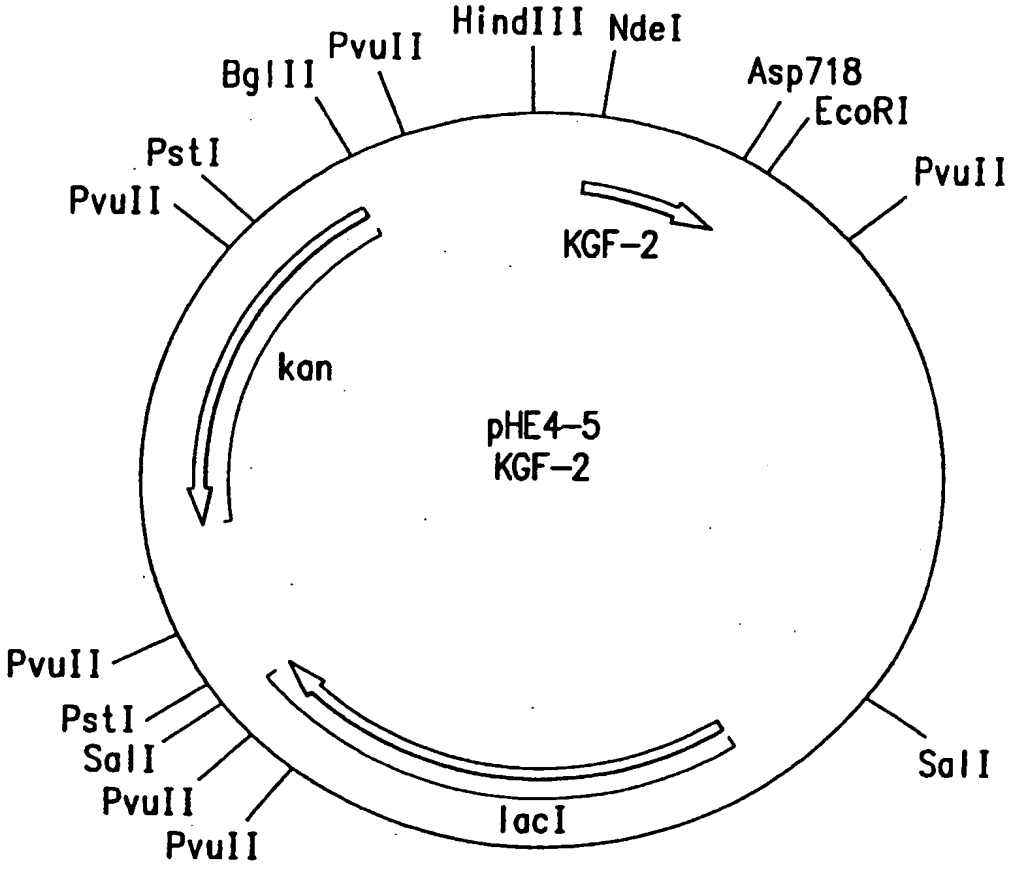

HindIII
NdeI
PvuII
BglII
Asp718
EcoRI
PstI
PvuII
PvuII
KGF-2
kan
pHE4-5
KGF-2
PvuII
PstI
SalI
PvuII
PvuII
lacI
SalI

FIG. 50

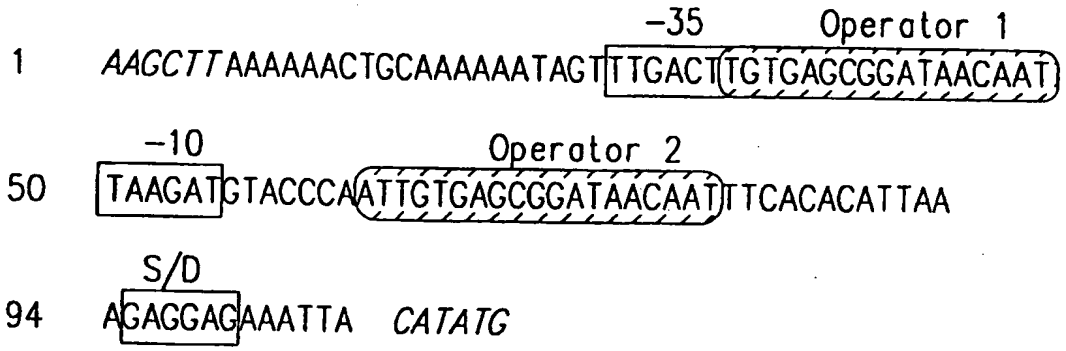

-35
Operator 1
1 AAGCTTAAAAAACTGCAAAAAATAGTTTGACTTGTGAGCGGATAACAAT
-10
Operator 2
50 TAAGATGTACCCAATTGTGAGCGGATAACAATTTCACACATTAA
S/D
94 AGAGGAGAAATTA CATATG

FIG. 51

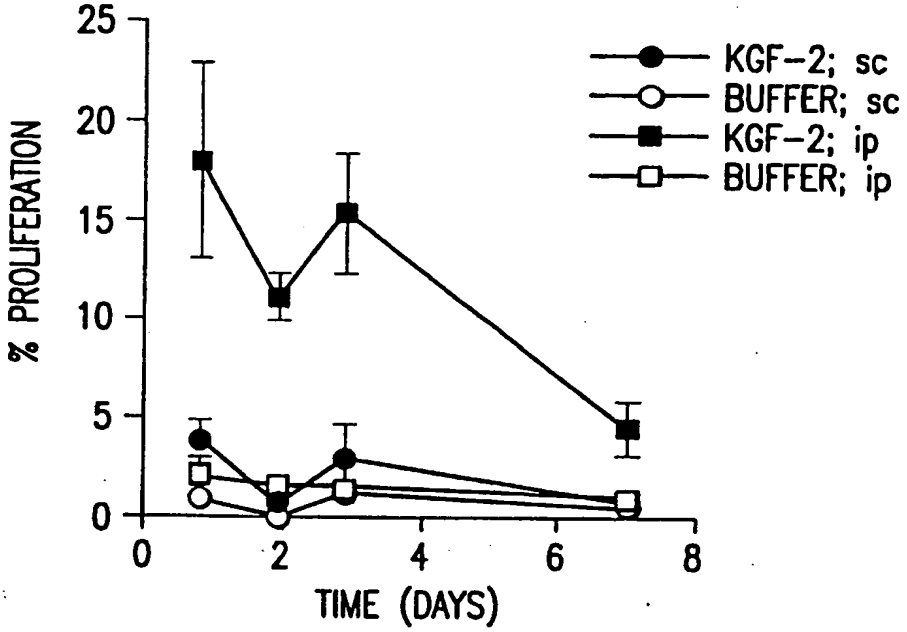

25
20
15
10
5
0
% PROLIFERATION
0
2
4
6
8
TIME (DAYS)
KGF-2; sc
BUFFER; sc
KGF-2; ip
BUFFER; ip

FIG. 52

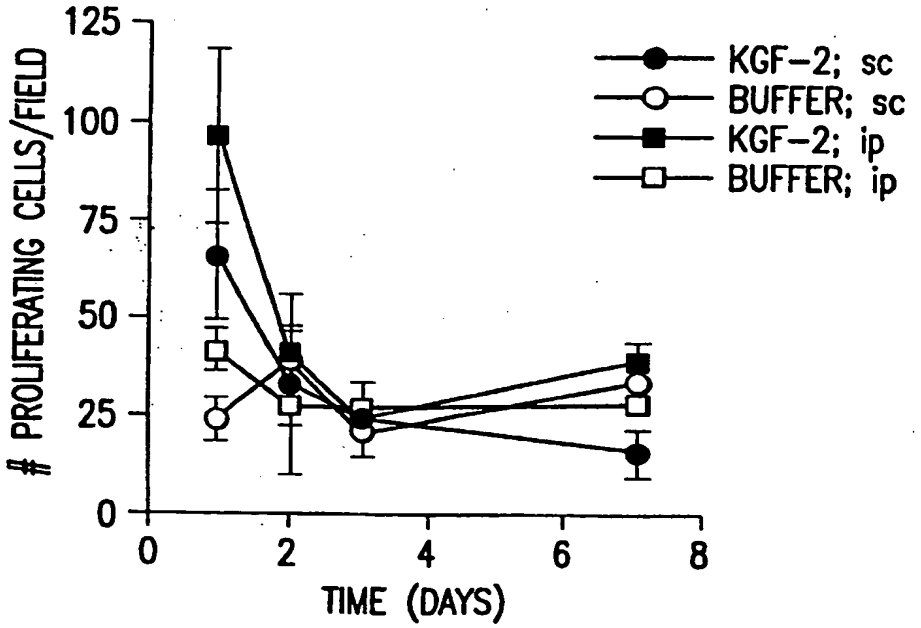

125
100
75
50
25
0
PROLIFERATING CELLS/FIELD
0
2
4
6
8
TIME (DAYS)
KGF-2; sc
BUFFER; sc
KGF-2; ip
BUFFER; ip

FIG. 53

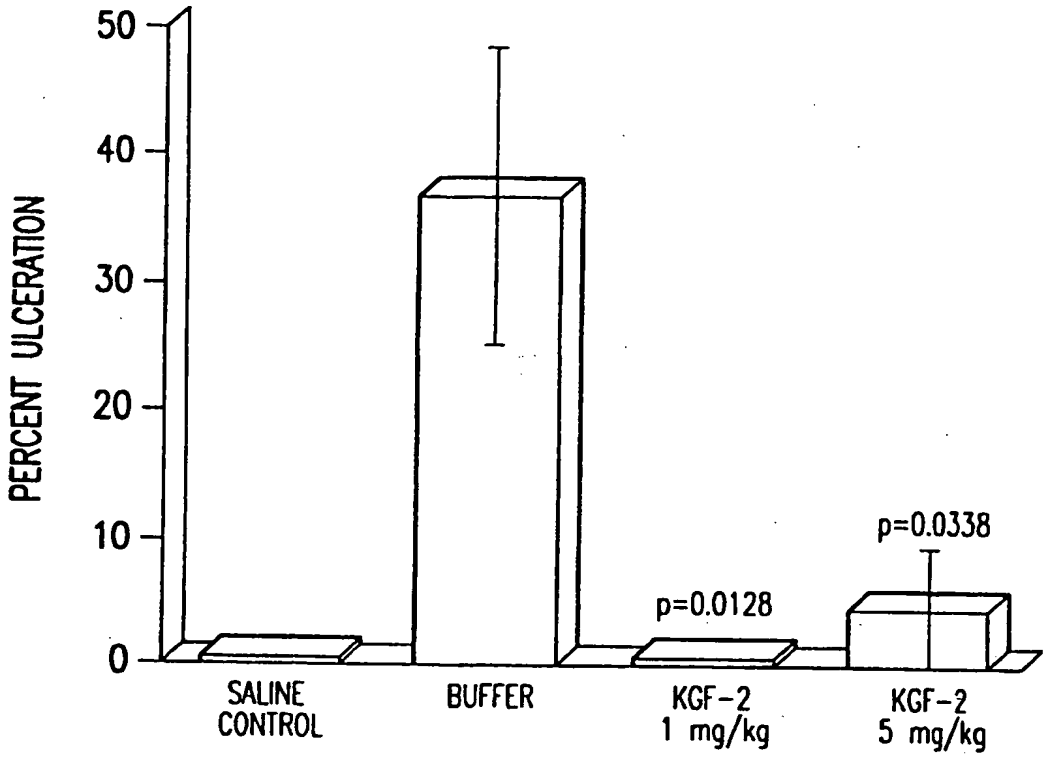

PERCENT ULCERATION
50
40
30
20
10
0
p=0.0338
p=0.0128
SALINE CONTROL
BUFFER
KGF-2 1 mg/kg
KGF-2 5 mg/kg

FIG. 54

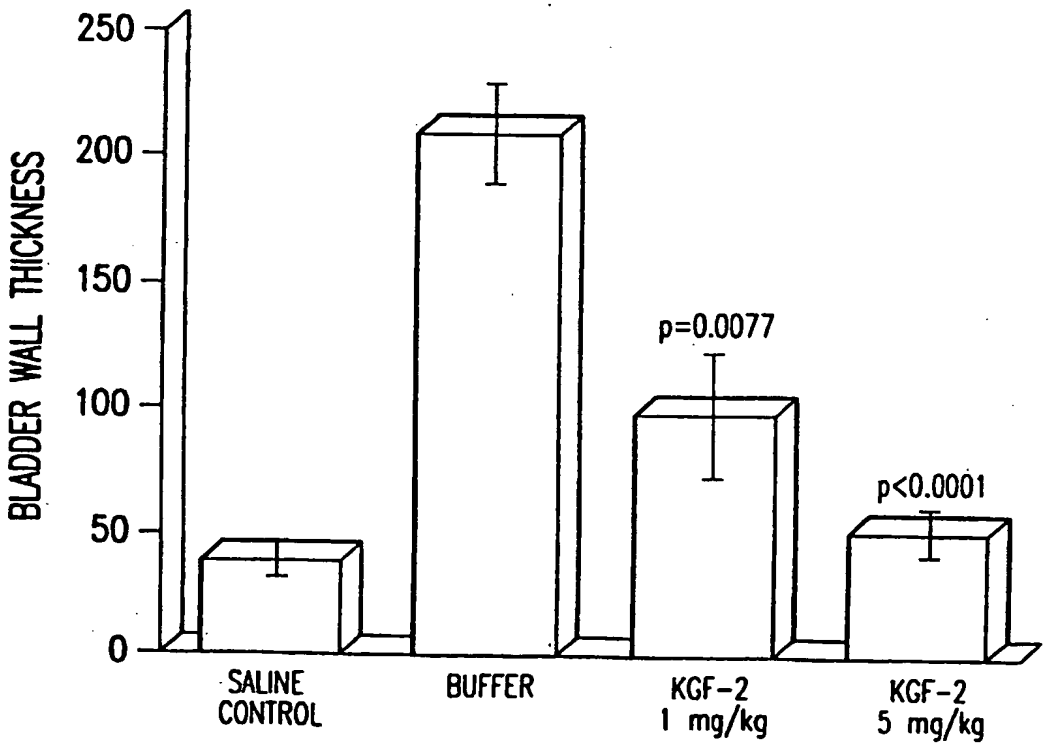

BLADDER WALL THICKNESS
250
200
150
100
50
0
p=0.0077
p<0.0001
SALINE CONTROL
BUFFER
KGF-2 1 mg/kg
KGF-2 5 mg/kg

FIG. 55

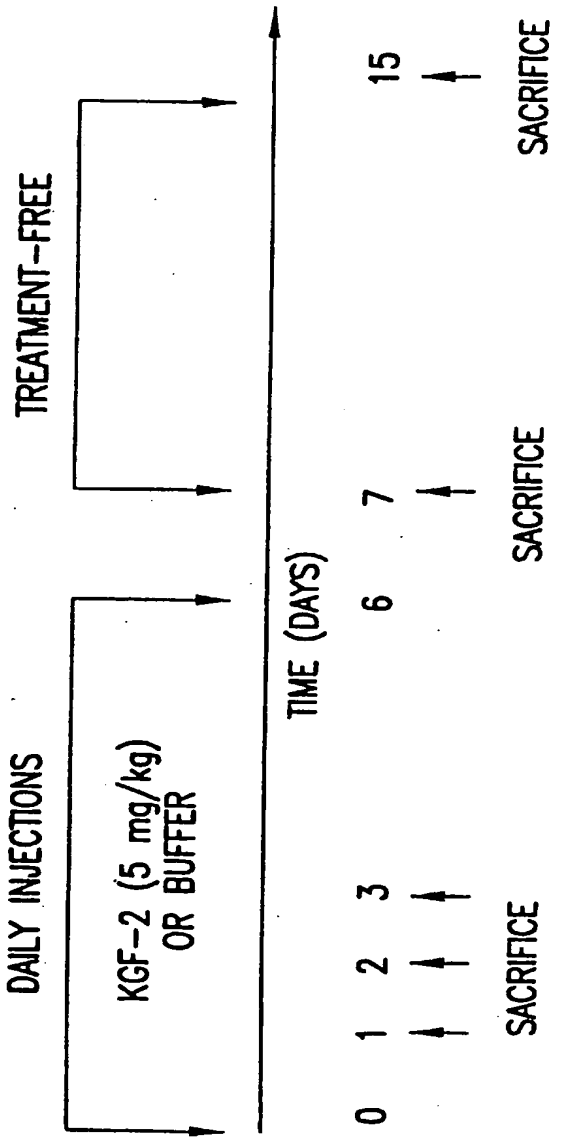

DAILY INJECTIONS
KGF-2 (5 mg/kg)
OR BUFFER
TREATMENT-FREE
TIME (DAYS)
0
1
2
3
6
7
15
SACRIFICE
SACRIFICE
SACRIFICE
SACRIFICE

FIG. 56

PROLIFERATION OF HEPATOCYTES FOLLOWING SYSTEMIC ADMINISTRATION OF KGF-2

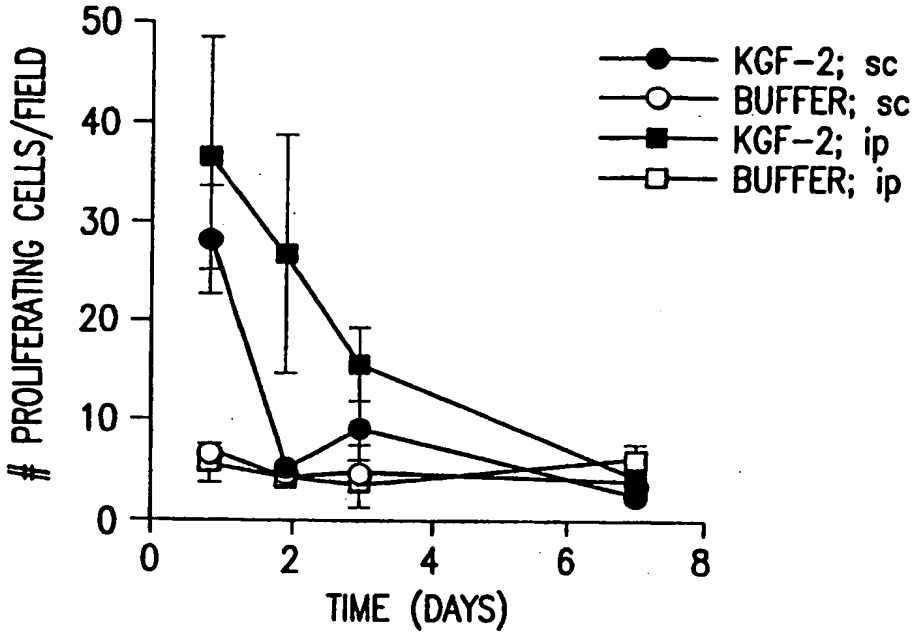


FIG. 57

PROLIFERATION OF PANCREATIC CELLS FOLLOWING SYSTEMIC ADMINISTRATION OF KGF-2

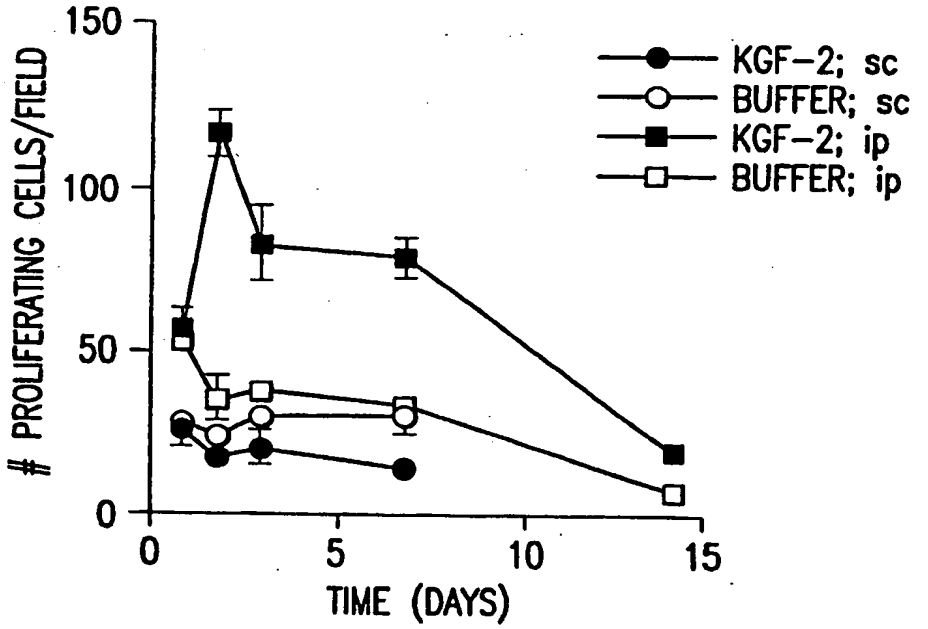


FIG. 58

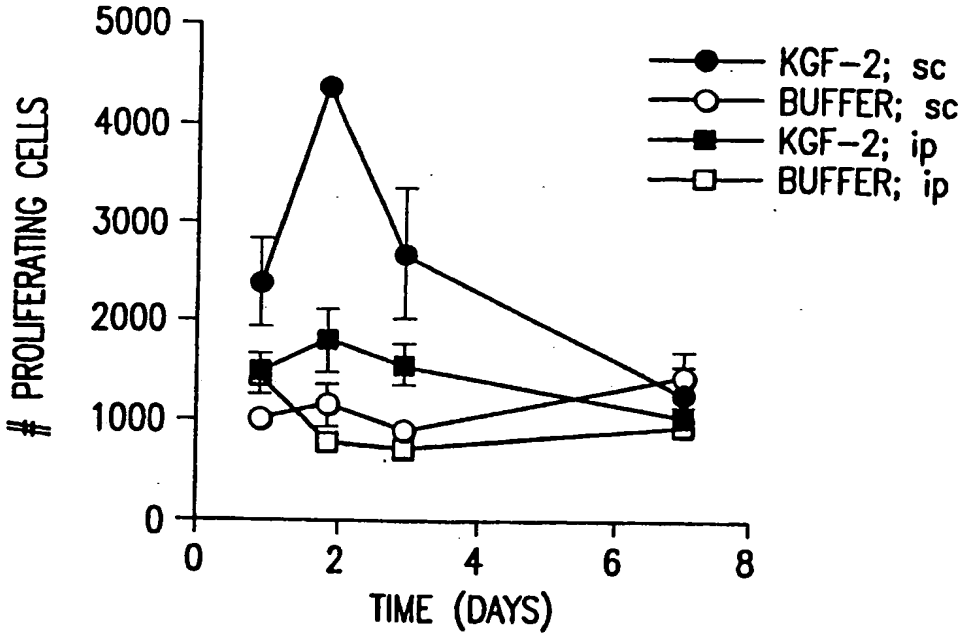

5000
4000
3000
2000
1000
0
PROLIFERATING CELLS
0
2
4
6
8
TIME (DAYS)
KGF-2; sc
BUFFER; sc
KGF-2; ip
BUFFER; ip

FIG. 59

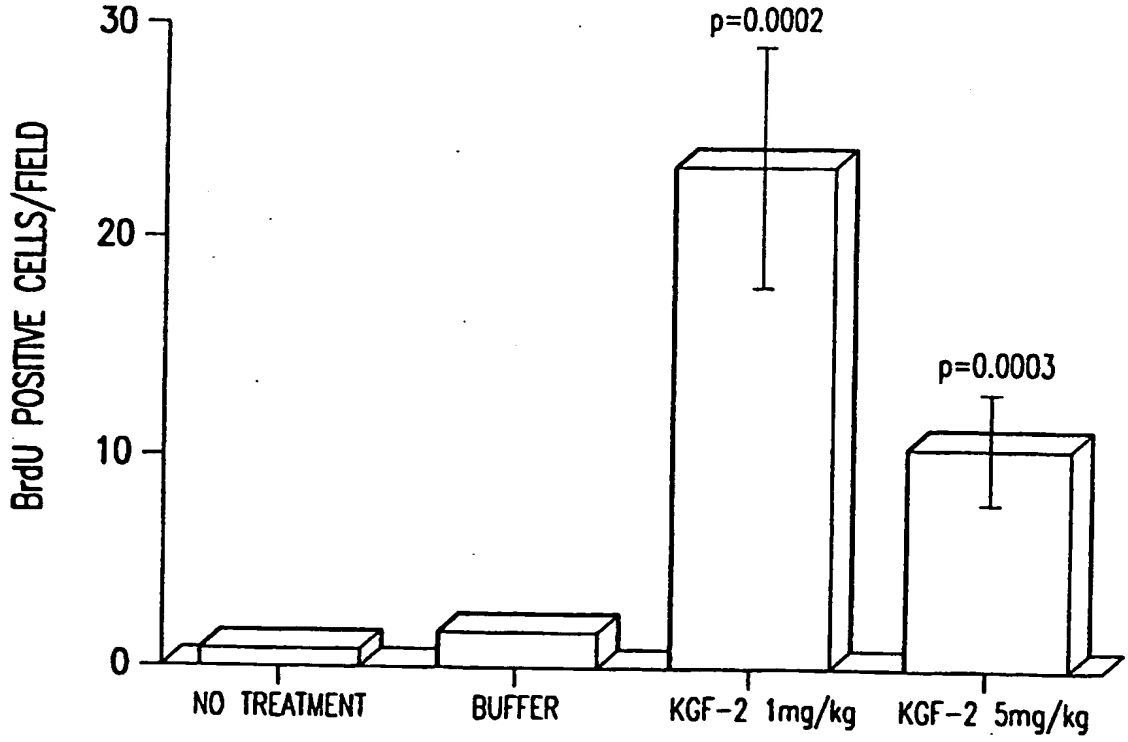

30
20
10
0
BrdU POSITIVE CELLS/FIELD
p=0.0002
p=0.0003
NO TREATMENT
BUFFER
KGF-2 1mg/kg
KGF-2 5mg/kg

FIG. 60

SEQUENCE LISTING

<110> Ruben, Steven M.
Jimenez, Pablo
Duan, D. Roxanne
Rampy, Mark A.
Mendrick, Donna
Zhang, Jun
Ni, Jian
Moore, Paul A.
Coleman, Timothy A.
Gruber, Joachim R.
Dillon, Patrick J.
Gentz, Reiner L.

<120> Keratinocyte Growth Factor-2

<130> 1488.036PC0P

<140>
<141>

<150> 60/259,853
<151> 2001-01-05

<150> 60/286,368
<151> 2001-04-26

<150> 60/331,168
<151> 2001-11-09

<160> 176

<170> PatentIn Ver. 2.1

<210> 1
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<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(624)

<400> 1

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atg tgg aaa tgg ata ctg aca cat tgt gcc tca gcc ttt ccc cac ctg   48
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
  1               5                  10                  15

ccc ggc tgc tgc tgc tgc tgc ttt ttg ttg ctg ttc ttg gtg tct tcc   96
Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30

gtc cct gtc acc tgc caa gcc ctt ggt cag gac atg gtg tca cca gag   144
Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45

gcc acc aac tct tct tcc tcc tcc ttc tcc tct cct tcc agc gcg gga   192
Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
```

```
     50                  55                  60

agg cat gtg cgg agc tac aat cac ctt caa gga gat gtc cgc tgg aga   240
Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
 65                  70                  75                  80

aag cta ttc tct ttc acc aag tac ttt ctc aag att gag aag aac ggg   288
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
                85                  90                  95

aag gtc agc ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag   336
Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110

ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc   384
Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125

aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa   432
Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140

gaa ttt aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga   480
Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160

tac aat acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg   528
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175

tat gtg gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca   576
Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190

cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca   624
Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205

tag                                                               627
```

<210> 2
<211> 208
<212> PRT
<213> Homo sapiens

<400> 2

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Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
  1               5                  10                  15

Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30

Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45

Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
    50                  55                  60

Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
 65                  70                  75                  80
```

```
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
                 85                  90                  95

Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110

Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125

Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140

Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160

Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175

Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190

Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205
```

<210> 3
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 3
ccccacatgt ggaaatggat actgacacat tgtgcc 36

<210> 4
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 4
cccaagcttc cacaaacgtt gccttcctct atgag 35

<210> 5
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 5

catgccatgg cgtgccaagc ccttggtcag gacatg 36

<210> 6
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 6
cccaagcttc cacaaacgtt gccttcctct atgag 35

<210> 7
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 7
gcgggatccg ccatcatgtg gaaatggata ctcac 35

<210> 8
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 8
gcgcggtacc acaaacgttg ccttcct 27

<210> 9
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 9
taacgaggat ccgccatcat gtggaaatgg atactgacac 40

<210> 10
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:

oligonucleotide

<400> 10
taagcactcg agtgagtgta ccaccattgg aagaaatg 38

<210> 11
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 11
attaaccctc actaaaggga ggccatgtgg aaatggatac tgacacattg tgcc 54

<210> 12
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 12
cccaagcttc cacaaacgtt gccttcctct atgag 35

<210> 13
<211> 206
<212> PRT
<213> Homo sapiens

<400> 13
Met Ser Gly Pro Gly Thr Ala Ala Val Ala Leu Leu Pro Ala Val Leu
1 5 10 15

Leu Ala Leu Leu Ala Pro Trp Ala Gly Arg Gly Gly Ala Ala Ala Pro
20 25 30

Thr Ala Pro Asn Gly Thr Leu Glu Ala Glu Leu Glu Arg Arg Trp Glu
35 40 45

Ser Leu Val Ala Leu Ser Leu Ala Arg Leu Pro Val Ala Ala Gln Pro
50 55 60

Lys Glu Ala Ala Val Gln Ser Gly Ala Gly Asp Tyr Leu Leu Gly Ile
65 70 75 80

Lys Arg Leu Arg Arg Leu Tyr Cys Asn Val Gly Ile Gly Phe His Leu
85 90 95

Gln Ala Leu Pro Asp Gly Arg Ile Gly Gly Ala His Ala Asp Thr Arg
100 105 110

Asp Ser Leu Leu Glu Leu Ser Pro Val Glu Arg Gly Val Val Ser Ile
115 120 125

```
Phe Gly Val Ala Ser Arg Phe Phe Val Ala Met Ser Ser Lys Gly Lys
    130                 135                 140

Leu Tyr Gly Ser Pro Phe Phe Thr Asp Glu Cys Thr Phe Lys Glu Ile
145                 150                 155                 160

Leu Leu Pro Asn Asn Tyr Asn Ala Tyr Glu Ser Tyr Lys Tyr Pro Gly
                165                 170                 175

Met Phe Ile Ala Leu Ser Lys Asn Gly Lys Thr Lys Lys Gly Asn Arg
            180                 185                 190

Val Ser Pro Thr Met Lys Val Thr His Phe Leu Pro Arg Leu
        195                 200                 205
```

<210> 14
<211> 198
<212> PRT
<213> Homo sapiens

<400> 14

```
Met Ser Arg Gly Ala Gly Arg Leu Gln Gly Thr Leu Trp Ala Leu Val
  1               5                  10                  15

Phe Leu Gly Ile Leu Val Gly Met Val Val Pro Ser Pro Ala Gly Thr
            20                  25                  30

Arg Ala Asn Asn Thr Leu Leu Asp Ser Arg Gly Trp Gly Thr Leu Leu
        35                  40                  45

Ser Arg Ser Arg Ala Gly Leu Ala Gly Glu Ile Ala Gly Val Asn Trp
    50                  55                  60

Glu Ser Gly Tyr Leu Val Gly Ile Lys Arg Gln Arg Arg Leu Tyr Cys
65                  70                  75                  80

Asn Val Gly Ile Gly Phe His Leu Gln Val Leu Pro Asp Gly Arg Ile
                85                  90                  95

Ser Gly Thr His Glu Glu Asn Pro Tyr Ser Leu Leu Glu Ile Ser Thr
            100                 105                 110

Val Glu Arg Gly Val Val Ser Leu Phe Gly Val Arg Ser Ala Leu Phe
        115                 120                 125

Val Ala Met Asn Ser Lys Gly Arg Leu Tyr Ala Thr Pro Ser Phe Gln
    130                 135                 140

Glu Glu Cys Lys Phe Arg Glu Thr Leu Leu Pro Asn Asn Tyr Asn Ala
145                 150                 155                 160

Tyr Glu Ser Asp Leu Tyr Gln Gly Thr Tyr Ile Ala Leu Ser Lys Tyr
                165                 170                 175

Gly Arg Val Lys Arg Gly Ser Lys Val Ser Pro Ile Met Thr Val Thr
            180                 185                 190

His Phe Leu Pro Arg Ile
        195
```

<210> 15
<211> 268
<212> PRT
<213> Homo sapiens

<400> 15

```
Met Ser Leu Ser Phe Leu Leu Leu Leu Phe Phe Ser His Leu Ile Leu
  1               5                  10                  15

Ser Ala Trp Ala His Gly Glu Lys Arg Leu Ala Pro Lys Gly Gln Pro
             20                  25                  30

Gly Pro Ala Ala Thr Asp Arg Asn Pro Arg Gly Ser Ser Ser Arg Gln
         35                  40                  45

Ser Ser Ser Ser Ala Met Ser Ser Ser Ser Ala Ser Ser Ser Pro Ala
     50                  55                  60

Ala Ser Leu Gly Ser Gln Gly Ser Gly Leu Glu Gln Ser Ser Phe Gln
 65                  70                  75                  80

Trp Ser Pro Ser Gly Arg Arg Thr Gly Ser Leu Tyr Cys Arg Val Gly
                 85                  90                  95

Ile Gly Phe His Leu Gln Ile Tyr Pro Asp Gly Lys Val Asn Gly Ser
            100                 105                 110

His Glu Ala Asn Met Leu Ser Val Leu Glu Ile Phe Ala Val Ser Gln
        115                 120                 125

Gly Ile Val Gly Ile Arg Gly Val Phe Ser Asn Lys Phe Leu Ala Met
    130                 135                 140

Ser Lys Lys Gly Lys Leu His Ala Ser Ala Lys Phe Thr Asp Asp Cys
145                 150                 155                 160

Lys Phe Arg Glu Arg Phe Gln Glu Asn Ser Tyr Asn Thr Tyr Ala Ser
                165                 170                 175

Ala Ile His Arg Thr Glu Lys Thr Gly Arg Glu Trp Tyr Val Ala Leu
            180                 185                 190

Asn Lys Arg Gly Lys Ala Lys Arg Gly Cys Ser Pro Arg Val Lys Pro
        195                 200                 205

Gln His Ile Ser Thr His Phe Leu Pro Arg Phe Lys Gln Ser Glu Gln
    210                 215                 220

Pro Glu Leu Ser Phe Thr Val Thr Val Pro Glu Lys Lys Asn Pro Pro
225                 230                 235                 240

Ser Pro Ile Lys Ser Lys Ile Pro Leu Ser Ala Pro Arg Lys Asn Thr
                245                 250                 255

Asn Ser Val Lys Tyr Arg Leu Lys Phe Arg Phe Gly
            260                 265
```

<210> 16
<211> 155
<212> PRT
<213> Homo sapiens

<400> 16
Met Ala Glu Gly Glu Ile Thr Thr Phe Thr Ala Leu Thr Glu Lys Phe
1 5 10 15

Asn Leu Pro Pro Gly Asn Tyr Lys Lys Pro Lys Leu Leu Tyr Cys Ser
20 25 30

Asn Gly Gly His Phe Leu Arg Ile Leu Pro Asp Gly Thr Val Asp Gly
35 40 45

Thr Arg Asp Arg Ser Asp Gln His Ile Gln Leu Gln Leu Ser Ala Glu
50 55 60

Ser Val Gly Glu Val Tyr Ile Lys Ser Thr Glu Thr Gly Gln Tyr Leu
65 70 75 80

Ala Met Asp Thr Asp Gly Leu Leu Tyr Gly Ser Gln Thr Pro Asn Glu
85 90 95

Glu Cys Leu Phe Leu Glu Arg Leu Glu Glu Asn His Tyr Asn Thr Tyr
100 105 110

Ile Ser Lys Lys His Ala Glu Lys Asn Trp Phe Val Gly Leu Lys Lys
115 120 125

Asn Gly Ser Cys Lys Arg Gly Pro Arg Thr His Tyr Gly Gln Lys Ala
130 135 140

Ile Leu Phe Leu Pro Leu Pro Val Ser Ser Asp
145 150 155

<210> 17
<211> 155
<212> PRT
<213> Homo sapiens

<400> 17
Met Ala Ala Gly Ser Ile Thr Thr Leu Pro Ala Leu Pro Glu Asp Gly
1 5 10 15

Gly Ser Gly Ala Phe Pro Pro Gly His Phe Lys Asp Pro Lys Arg Leu
20 25 30

Tyr Cys Lys Asn Gly Gly Phe Phe Leu Arg Ile His Pro Asp Gly Arg
35 40 45

Val Asp Gly Val Arg Glu Lys Ser Asp Pro His Ile Lys Leu Gln Leu
50 55 60

Gln Ala Glu Glu Arg Gly Val Val Ser Ile Lys Gly Val Cys Ala Asn
65 70 75 80

Arg Tyr Leu Ala Met Lys Glu Asp Gly Arg Leu Leu Ala Ser Lys Cys
85 90 95

Val Thr Asp Glu Cys Phe Phe Phe Glu Arg Leu Glu Ser Asn Asn Tyr
100 105 110

Asn Thr Tyr Arg Ser Arg Lys Tyr Thr Ser Trp Tyr Val Ala Leu Lys
115 120 125

```
Arg Thr Gly Gln Tyr Lys Leu Gly Ser Lys Thr Gly Pro Gly Gln Lys
    130                 135                 140

Ala Ile Leu Phe Leu Pro Met Ser Ala Lys Ser
145                 150                 155


<210> 18
<211> 208
<212> PRT
<213> Homo sapiens

<400> 18
Met Ala Pro Leu Gly Glu Val Gly Asn Tyr Phe Gly Val Gln Asp Ala
  1               5                  10                  15

Val Pro Phe Gly Asn Val Pro Val Leu Pro Val Asp Ser Pro Val Leu
            20                  25                  30

Leu Ser Asp His Leu Gly Gln Ser Glu Ala Gly Gly Leu Pro Arg Gly
        35                  40                  45

Pro Ala Val Thr Asp Leu Asp His Leu Lys Gly Ile Leu Arg Arg Arg
    50                  55                  60

Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Glu Ile Phe Pro Asn Gly
65                  70                  75                  80

Thr Ile Gln Gly Thr Arg Lys Asp His Ser Arg Phe Gly Ile Leu Glu
                85                  90                  95

Phe Ile Ser Ile Ala Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser
            100                 105                 110

Gly Leu Tyr Leu Gly Met Asn Glu Lys Gly Glu Leu Tyr Gly Ser Glu
        115                 120                 125

Lys Leu Thr Gln Glu Cys Val Phe Arg Glu Gln Phe Glu Glu Asn Trp
    130                 135                 140

Tyr Asn Thr Tyr Ser Ser Asn Leu Tyr Lys His Val Asp Thr Gly Arg
145                 150                 155                 160

Arg Tyr Tyr Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Glu Gly Thr
                165                 170                 175

Arg Thr Lys Arg His Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val
            180                 185                 190

Asp Pro Asp Lys Val Pro Glu Leu Tyr Lys Asp Ile Leu Ser Gln Ser
        195                 200                 205


<210> 19
<211> 194
<212> PRT
<213> Homo sapiens

<400> 19
```

```
Met His Lys Trp Ile Leu Thr Trp Ile Leu Pro Thr Leu Leu Tyr Arg
 1               5                  10                  15

Ser Cys Phe His Ile Ile Cys Leu Val Gly Thr Ile Ser Leu Ala Cys
            20                  25                  30

Asn Asp Met Thr Pro Glu Gln Met Ala Thr Asn Val Asn Cys Ser Ser
        35                  40                  45

Pro Glu Arg His Thr Arg Ser Tyr Asp Tyr Met Glu Gly Gly Asp Ile
    50                  55                  60

Arg Val Arg Arg Leu Phe Cys Arg Thr Gln Trp Tyr Leu Arg Ile Asp
65                  70                  75                  80

Lys Arg Gly Lys Val Lys Gly Thr Gln Glu Met Lys Asn Asn Tyr Asn
                85                  90                  95

Ile Met Glu Ile Arg Thr Val Ala Val Gly Ile Val Ala Ile Lys Gly
            100                 105                 110

Val Glu Ser Glu Phe Tyr Leu Ala Met Asn Lys Glu Gly Lys Leu Tyr
        115                 120                 125

Ala Lys Lys Glu Cys Asn Glu Asp Cys Asn Phe Lys Glu Leu Ile Leu
    130                 135                 140

Glu Asn His Tyr Asn Thr Tyr Ala Ser Ala Lys Trp Thr His Asn Gly
145                 150                 155                 160

Gly Glu Met Phe Val Ala Leu Asn Gln Lys Gly Ile Pro Val Arg Gly
                165                 170                 175

Lys Lys Thr Lys Lys Glu Gln Lys Thr Ala His Phe Leu Pro Met Ala
            180                 185                 190

Ile Thr
```

<210> 20
<211> 208
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
 1               5                  10                  15

Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30

Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45

Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
    50                  55                  60

Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
65                  70                  75                  80

Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
```

```
                85                  90                  95

Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110

Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125

Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140

Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160

Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175

Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190

Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205
```

<210> 21
<211> 239
<212> PRT
<213> Homo sapiens

<400> 21

```
Met Gly Leu Ile Trp Leu Leu Leu Leu Ser Leu Leu Glu Pro Gly Trp
  1               5                  10                  15

Pro Ala Ala Gly Pro Gly Ala Arg Leu Arg Arg Asp Ala Gly Gly Arg
             20                  25                  30

Gly Gly Val Tyr Glu His Leu Gly Gly Ala Pro Arg Arg Arg Lys Leu
         35                  40                  45

Tyr Cys Ala Thr Lys Tyr His Leu Gln Leu His Pro Ser Gly Arg Val
     50                  55                  60

Asn Gly Ser Leu Glu Asn Ser Ala Tyr Ser Ile Leu Glu Ile Thr Ala
 65                  70                  75                  80

Val Glu Val Gly Ile Val Ala Ile Arg Gly Leu Phe Ser Gly Arg Tyr
                85                  90                  95

Leu Ala Met Asn Lys Arg Gly Arg Leu Tyr Ala Ser Glu His Tyr Ser
            100                 105                 110

Ala Glu Cys Glu Phe Val Glu Arg Ile His Glu Leu Gly Tyr Asn Thr
        115                 120                 125

Tyr Ala Ser Arg Leu Tyr Arg Thr Val Ser Ser Thr Pro Gly Ala Arg
    130                 135                 140

Arg Gln Pro Ser Ala Glu Arg Leu Trp Tyr Val Ser Val Asn Gly Lys
145                 150                 155                 160
```

```
Gly Arg Pro Arg Arg Gly Phe Lys Thr Arg Arg Thr Gln Lys Ser Ser
                165                 170                 175

Leu Phe Leu Pro Arg Val Leu Asp His Arg Asp His Glu Met Val Arg
            180                 185                 190

Gln Leu Gln Ser Gly Leu Pro Arg Pro Pro Gly Lys Gly Val Gln Pro
        195                 200                 205

Arg Arg Arg Arg Gln Lys Gln Ser Pro Asp Asn Leu Glu Pro Ser His
    210                 215                 220

Val Gln Ala Ser Arg Leu Gly Ser Gln Leu Glu Ala Ser Ala His
225                 230                 235
```

<210> 22
<211> 268
<212> PRT
<213> Homo sapiens

<400> 22

```
Met Gly Ser Pro Arg Ser Ala Leu Ser Cys Leu Leu Leu His Leu Leu
  1               5                  10                  15

Val Leu Cys Leu Gln Ala Gln Val Arg Ser Ala Ala Gln Lys Arg Gly
             20                  25                  30

Pro Gly Ala Gly Asn Pro Ala Asp Thr Leu Gly Gln Gly His Glu Asp
         35                  40                  45

Arg Pro Phe Gly Gln Arg Ser Arg Ala Gly Lys Asn Phe Thr Asn Pro
     50                  55                  60

Ala Pro Asn Tyr Pro Glu Glu Gly Ser Lys Glu Gln Arg Asp Ser Val
 65                  70                  75                  80

Leu Pro Lys Val Thr Gln Arg His Val Arg Glu Gln Ser Leu Val Thr
                 85                  90                  95

Asp Gln Leu Ser Arg Arg Leu Ile Arg Thr Tyr Gln Leu Tyr Ser Arg
            100                 105                 110

Thr Ser Gly Lys His Val Gln Val Leu Ala Asn Lys Arg Ile Asn Ala
        115                 120                 125

Met Ala Glu Asp Gly Asp Pro Phe Ala Lys Leu Ile Val Glu Thr Asp
    130                 135                 140

Thr Phe Gly Ser Arg Val Arg Val Arg Gly Ala Glu Thr Gly Leu Tyr
145                 150                 155                 160

Ile Cys Met Asn Lys Lys Gly Lys Leu Ile Ala Lys Ser Asn Gly Lys
                165                 170                 175

Gly Lys Asp Cys Val Phe Thr Glu Ile Val Leu Glu Asn Asn Tyr Thr
            180                 185                 190

Ala Leu Gln Asn Ala Lys Tyr Glu Gly Trp Tyr Met Ala Phe Thr Arg
        195                 200                 205

Lys Gly Arg Pro Arg Lys Gly Ser Lys Thr Arg Gln His Gln Arg Glu
```

```
    210                 215                 220

Val His Phe Met Lys Arg Leu Pro Arg Gly His His Thr Thr Glu Gln
225                 230                 235                 240

Ser Leu Arg Phe Glu Phe Leu Asn Tyr Pro Pro Phe Thr Arg Ser Leu
                245                 250                 255

Arg Gly Ser Gln Arg Thr Trp Ala Pro Glu Pro Arg
            260                 265
```

<210> 23
<211> 4177
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (593)..(1216)

<400> 23

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ggaattccgg gaagagaggg aagaaaacaa cggcgactgg gcagctgcct ccacttctga 60

caactccaaa gggatatact tgtagaagtg gctcgcaggc tggggctccg cagagagaga 120

ccagaaggtg ccaaccgcag aggggtgcag atatctcccc ctattcccca ccccacctcc 180

cttgggtttt gttcaccgtg ctgtcatctg tttttcagac ctttttggca tctaacatgg 240

tgaagaaagg agtaaagaag agaacaaagt aactcctggg ggagcgaaga gcgctggtga 300

ccaacaccac caacgccacc accagctcct gctgctgcgg ccacccacgt ccaccattta 360

ccgggaggct ccagaggcgt aggcagcgga tccgagaaag gagcgagggg agtcagccgg 420

cttttccgag gagttatgga tgttggtgca ttcacttctg gccagatccg cgcccagagg 480

gagctaacca gcagccacca cctcgagctc tctccttgcc ttgcatcggg tcttaccctt 540

ccagtatgtt ccttctgatg agacaatttc cagtgccgag agtttcagta ca atg tgg 598
                                                        Met Trp
                                                          1

aaa tgg ata ctg aca cat tgt gcc tca gcc ttt ccc cac ctg ccc ggc   646
Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro Gly
          5                  10                  15

tgc tgc tgc tgc tgc ttt ttg ttg ctg ttc ttg gtg tct tcc gtc cct   694
Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val Pro
     20                  25                  30

gtc acc tgc caa gcc ctt ggt cag gac atg gtg tca cca gag gcc acc   742
Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 35                  40                  45                  50

aac tct tct tcc tcc tcc ttc tcc tct cct tcc agc gcg gga agg cat   790
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
                 55                  60                  65

gtg cgg agc tac aat cac ctt caa gga gat gtc cgc tgg aga aag cta   838
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
```

```
                70                  75                  80

ttc tct ttc acc aag tac ttt ctc aag att gag aag aac ggg aag gtc   886
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
         85                  90                  95

agc ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca   934
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
    100                 105                 110

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat   982
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
115                 120                 125                 130

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt  1030
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
                135                 140                 145

aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat  1078
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
            150                 155                 160

acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg  1126
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
        165                 170                 175

gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg  1174
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
    180                 185                 190

aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca          1216
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
195                 200                 205

tagaggaagg caacgtttgt ggatgcagta aaaccaatgg ctcttttgcc aagaatagtg 1276

gatattcttc atgaagacag tagattgaaa ggcaaagaca cgttgcagat gtctgcttgc 1336

ttaaaagaaa gccagccttt gaaggttttt gtattcactg ctgacatatg atgttctttt 1396

aattagttct gtgtcatgtc ttataatcaa gatataggca gatcgaatgg gatagaagtt 1456

attcccaagt gaaaaacatt gtggctgggt tttttgttgt tgttgtcaag tttttgtttt 1516

taaacctctg agatagaact taaaggacat agaacaatct gttgaaagaa cgatcttcgg 1576

gaaagttatt tatggaatac gaactcatat caaagacttc attgctcatt caagcctaat 1636

gaatcaatga acagtaatac gtgcaagcat ttactggaaa gcacttgggt catatcatat 1696

gcacaaccaa aggagttctg gatgtggtct catggaataa ttgaatagaa tttaaaaata 1756

taaacatgtt agtgtgaaac tgttctaaca atacaaatag tatggtatgc ttgtgcattc 1816

tgccttcatc cctttctatt tctttctaag ttatttattt aataggatgt taaatatctt 1876

ttggggtttt aaagagtatc tcagcagctg tcttctgatt tatcttttct ttttattcag 1936

cacaccacat gcatgttcac gacaaagtgt ttttaaaact tggcgaacac ttcaaaaata 1996

ggagttggga ttagggaagc agtatgagtg cccgtgtgct atcagttgac ttaatttgca 2056
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cttctgcagt aataaccatc aacaataaat atggcaatgc tgtgccatgg cttgagtgag 2116

agatgtctgc tatcatttga aaacatatat tactctcgag gcttcctgtc tcaagaaata 2176

gaccagaagg ccaaattctt ctctttcaat acatcagttt gcctccaaga atatactaaa 2236

aaaaggaaaa ttaattgcta aatacattta aatagcctag cctcattatt tactcatgat 2296

ttcttgccaa atgtcatggc ggtaaagagg ctgtccacat ctctaaaaac cctctgtaaa 2356

ttccacataa tgcatctttc ccaaaggaac tataaagaat ttggtatgaa gcgcaactct 2416

cccaggggct taaactgagc aaatcaaata tatactggta tatgtgtaac catatacaaa 2476

aacctgttct agctgtatga tctagtcttt acaaaaccaa ataaaacttg ttttctgtaa 2536

atttaaagag ctttacaagg ttccataatg taaccatatc aaaattcatt ttgttagagc 2596

acgtatagaa aagagtacat aagagtttac caatçatcat cacattgtat tccactaaat 2656

aaatacataa gccttatttg cagtgtctgt agtgatttta aaaatgtaga aaaatactat 2716

ttgttctaaa tacttttaag caataactat aatagtatat tgatgctgca gttttatctt 2776

catatttctt gttttgaaaa agcattttat tgtttggaca cagtattttg gtacaaaaaa 2836

aaagactcac taaatgtgtc ttactaaagt ttaacctttg gaaatgctgg cgttctgtga 2896

ttctccaaca aacttatttg tgtcaatact taaccagcac ttccagttaa tctgttattt 2956

ttaaaaattg ctttattaag aaatttttg tataatccca taaaaggtca tatttttccc 3016

attcttcaaa aaaactgtat ttcagaagaa acacatttga ggcactgtct tttggcttat 3076

agtttaaatt gcatttcatc atactttgct tccaacttgc tttttggcaa atgagattat 3136

aaaaatgttt aatttttgtg gttggaatct ggatgttaaa atttaattgg taactcagtc 3196

tgtgagctat aatgtaatgc attcctatcc aaactaggta tctttttttc ctttatgttg 3256

aaataataat ggcacctgac acatagacat agaccaccca caacctaaat taaatgtttg 3316

gtaagacaaa tacacattgg atgaccacag taacagcaaa cagggcacaa actggattct 3376

tatttcacat agacatttag attactaaag agggctatgt gtaaacagtc atcattatag 3436

tactcaagac actaaaacag cttctagcca aatatattaa agcttgcaga ggccaaaaat 3496

agaaaacatc tcccctgtct ctcccacatt tccctcacag aaagacaaaa aacctgcctg 3556

gtgcagtagc tcacacctgt aatcccagca gtttgggaga ctgtgggaag atggcttgag 3616

tccaggagtt ctagacaggc ctgagaaacc tagtgagaca tccttctctt aaacaaaaca 3676

aaacaaaaca aatgtagcca tgcgtggtgg catatacctg tggtcccaac tactcaggag 3736

gctgaaacgg aaggatctct tgggccccag gagtttgagg ctgcagtgag ctataatctt 3796

gccattgcac tccagcctgg gtgaaaaaga gccagaaaga aaggaaagag agaaaagaga 3856

aaagaaagag agaaaagaca gaaagacagg aaggaaggaa ggaaggaagg aaggaaggaa 3916

ggaagcaagg aaagaaggaa ggaaggaaag aagggaggga aggaaggaga gagaaagaaa 3976

gattgtttgg taaggagtaa tgacattctc ttgcatttaa aagtggcata tttgcttgaa 4036

atggaaatag aattctggtc ccttttgcaa ctactgaaga aaaaaaaaag cagtttcagc 4096

cctgaatgtt gtagatttga aaaaaaaaaa aaaaaaactc gagggggggc ccgtacccaa 4156

ttcgccctat agtgagtcgt a 4177

<210> 24
<211> 208
<212> PRT
<213> Homo sapiens

<400> 24

Met	Trp	Lys	Trp	Ile	Leu	Thr	His	Cys	Ala	Ser	Ala	Phe	Pro	His	Leu
1				5				10					15		
Pro	Gly	Cys	Cys	Cys	Cys	Cys	Phe	Leu	Leu	Leu	Phe	Leu	Val	Ser	Ser
			20					25				30			
Val	Pro	Val	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu
		35					40					45			
Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Ser	Ser	Ala	Gly
	50					55					60				
Arg	His	Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg
65					70					75					80
Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly
				85					90					95	
Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu
			100					105					110		
Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser
		115					120					125			
Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys
	130					135					140				
Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly
145					150					155					160
Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met
				165					170					175	
Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr
			180					185					190		
Arg	Arg	Lys	Asn	Thr	Ser	Ala	His	Phe	Leu	Pro	Met	Val	Val	His	Ser
		195					200					205			

<210> 25
<211> 31
<212> PRT
<213> Homo sapiens

<400> 25
Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser
1 5 10 15

Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser Tyr Asn
20 25 30

<210> 26
<211> 19
<212> PRT
<213> Homo sapiens

<400> 26
Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys
1 5 10 15

Pro Tyr Ser

<210> 27
<211> 30
<212> PRT
<213> Homo sapiens

<400> 27
Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
1 5 10 15

Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr
20 25 30

<210> 28
<211> 19
<212> PRT
<213> Homo sapiens

<400> 28
Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn
1 5 10 15

Thr Ser Ala

<210> 29
<211> 555
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(552)

<220>
<223> Description of Artificial Sequence: pQE60-Cys37
construct

<400> 29
atg aga gga tcg cat cac cat cac cat cac gga tcc tgc cag gct ctg 48

```
Met Arg Gly Ser His His His His His His Gly Ser Cys Gln Ala Leu
  1               5                  10                  15

ggt cag gac atg gtt tct ccg gaa gct acc aac tct tcc tct tcc tct   96
Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser
            20                  25                  30

ttc tct tcc ccg tct tcc gct ggt cgt cac gtt cgt tct tac aac cac   144
Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser Tyr Asn His
        35                  40                  45

ctg cag ggt gac gtt cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac   192
Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr
    50                  55                  60

ttc ctg aaa atc gaa aaa aac ggt aaa gtt tct ggg acc aag aag gag   240
Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu
65                  70                  75                  80

aac tgc ccg tac agc atc ctg gag ata aca tca gta gaa atc gga gtt   288
Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val
                85                  90                  95

gtt gcc gtc aaa gcc att aac agc aac tat tac tta gcc atg aac aag   336
Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys
            100                 105                 110

aag ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg   384
Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
        115                 120                 125

aag gag agg ata gag gaa aat gga tac aat acc tat gca tca ttt aac   432
Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
    130                 135                 140

tgg cag cat aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga   480
Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
145                 150                 155                 160

gct cca agg aga gga cag aaa aca cga agg aaa aac acc tct gct cac   528
Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
                165                 170                 175

ttt ctt cca atg gtg gta cac tca tag                              555
Phe Leu Pro Met Val Val His Ser
            180
```

<210> 30
<211> 184
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: pQE60-Cys37 construct

<400> 30

```
Met Arg Gly Ser His His His His His His Gly Ser Cys Gln Ala Leu
  1               5                  10                  15

Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser
            20                  25                  30
```

```
Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser Tyr Asn His
         35                  40                  45

Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr
     50                  55                  60

Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu
 65                  70                  75                  80

Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val
                 85                  90                  95

Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys
            100                 105                 110

Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
        115                 120                 125

Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
    130                 135                 140

Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
145                 150                 155                 160

Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
                165                 170                 175

Phe Leu Pro Met Val Val His Ser
            180
```

<210> 31
<211> 84
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 31
atgtggaaat ggatactgac ccactgcgct tctgctttcc cgcacctgcc gggttgctgc 60
tgctgctgct tcctgctgct gttc 84

<210> 32
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 32
ccggagaaac catgtcctga cccagagcct ggcaggtaac cggaacagaa gaaaccagga 60
acagcagcag gaagcagcag ca 82

<210> 33
<211> 80

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 33
gggtcaggac atggtttctc cggaagctac caactcttct tcttcttctt tctcttctcc 60
gtcttctgct ggtcgtcacg 80

<210> 34
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 34
ggtgaaagag aacagtttac gccaacgaac gtcaccctgc aggtggttgt aagaacgaac 60
gtgacgacca gcagaagacg g 81

<210> 35
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 35
cgttggcgta aactgttctc tttcaccaaa tacttcctga aaatcgaaaa aaacggtaaa 60
gtttctggga ccaaa 75

<210> 36
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 36
tttggtccca gaaactttac cgtttttttc gattttcag 39

<210> 37
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 37
aaaggatcca tgtggaaatg gatactgacc cactgc 36

<210> 38
<211> 627
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (1)..(627)

<400> 38
atg tgg aaa tgg ata ctg acc cac tgc gct tct gct ttc ccg cac ctg 48
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
1 5 10 15

ccg ggt tgc tgc tgc tgc tgc ttc ctg ctg ctg ttc ctg gtt tct tct 96
Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
20 25 30

gtt ccg gtt acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa 144
Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
35 40 45

gct acc aac tct tcc tct tcc tct ttc tct tcc ccg act tcc gct ggt 192
Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Thr Ser Ala Gly
50 55 60

cgt cac gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt 240
Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
65 70 75 80

aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt 288
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
85 90 95

aaa gtt tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag 336
Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
100 105 110

ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc 384
Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
115 120 125

aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa 432
Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
130 135 140

gaa ttt aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga 480
Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145 150 155 160

tac aat acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg 528
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
165 170 175

tat gtg gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca 576
Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
180 185 190

```
cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca   624
Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205

tag                                                               627
```

<210> 39
<211> 208
<212> PRT
<213> Escherichia coli

<400> 39

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Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
  1               5                  10                  15
Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30
Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45
Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Thr Ser Ala Gly
    50                  55                  60
Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
65                  70                  75                  80
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
                85                  90                  95
Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110
Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125
Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140
Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175
Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190
Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205
```

<210> 40
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 40

```
tttcatgact tgtcaagctc tgggtcaaga tatggttc                         38
```

<210> 41
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 41
gcccaagctt ccacaaacgt tgccttcc 28

<210> 42
<211> 525
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (1)..(522)

<400> 42

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atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc   48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1               5                  10                  15

aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac   96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20                  25                  30

gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg   144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt   192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca   240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat   288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt   336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat   384
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
        115                 120                 125

acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg   432
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
    130                 135                 140

gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg   480
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145                 150                 155                 160

aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca tag       525
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
                165                 170
```

<210> 43
<211> 174
<212> PRT

<213> Escherichia coli

<400> 43

```
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1               5                  10                  15

Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20                  25                  30

Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
        115                 120                 125

Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
    130                 135                 140

Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145                 150                 155                 160

Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
                165                 170
```

<210> 44
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 44
tcagtgaatt cattaaagag gagaaattaa tcatgacttg ccagg 45

<210> 45
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 45
tcatgacttg ccaggcactg ggtcaagaca tggtttcccc ggaagcta 48

<210> 46
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 46
gcttcagcag cccatctagc gcaggtcgtc acgttcgctc ttacaacc 48

<210> 47
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 47
gttcgttggc gcaaactgtt cagctttacc aagtacttcc tgaaaatc 48

<210> 48
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 48
tcgaaaaaaa cggtaaagtt tctgggac 28

<210> 49
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 49
gatgggctgc tgaagctaga gctggagctg ttggtagctt ccggggaa 48

<210> 50
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 50
aacagtttgc gccaacgaac atcaccctgt aagtggttgt aagag 45

<210> 51
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 51
ttcttggtcc cagaaacttt accgtttttt tcgattttca ggaagta 47

<210> 52
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 52
ttcttggtcc cagaaacttt accg 24

<210> 53
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 53
agatcaggct tctattatta tgagtgtacc accattggaa gaaag 45

<210> 54
<211> 525
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (1)..(522)

<400> 54
atg act tgc cag gca ctg ggt caa gac atg gtt tcc ccg gaa gct acc 48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
1 5 10 15

aac agc tcc agc tct agc ttc agc agc cca tct agc gca ggt cgt cac 96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
20 25 30

gtt cgc tct tac aac cac tta cag ggt gat gtt cgt tgg cgc aaa ctg 144

```
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

ttc agc ttt acc aag tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt   192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca   240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat   288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt   336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat   384
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
        115                 120                 125

acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg   432
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
    130                 135                 140

gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg   480
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145                 150                 155                 160

aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca tag       525
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
                165                 170
```

<210> 55
<211> 174
<212> PRT
<213> Escherichia coli

<400> 55

```
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1               5                  10                  15

Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20                  25                  30

Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110
```

Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
115 120 125

Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
130 135 140

Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145 150 155 160

Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
165 170

<210> 56
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 56
ggaccctcat gacctgccag gctctgggtc aggac 35

<210> 57
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 57
ggacagccat ggctggtcgt cacgttcg 28

<210> 58
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 58
ggacagccat ggttcgttgg cgtaaactg 29

<210> 59
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 59
ggacagccat ggaaaaaaac ggtaaagttt c 31

<210> 60
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 60
ggacccccat ggagaactgc ccgtagagc 29

<210> 61
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 61
ggacccccat ggtcaaagcc attaacagca ac 32

<210> 62
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 62
ggacccccat ggggaaactc tatggctcaa aag 33

<210> 63
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 63
ctgcccaagc ttattatgag tgtaccacca ttggaag 37

<210> 64
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 64
ctgcccaagc ttattacttc agcttacagt cattgt 36

<210> 65
<211> 525

<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(522)

<400> 65
```
atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc   48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 1               5                  10                  15

aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac   96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
            20                  25                  30

gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg  144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
        35                  40                  45

ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt  192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
    50                  55                  60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca  240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
65                  70                  75                  80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat  288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                85                  90                  95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt  336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat  384
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
        115                 120                 125

acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg  432
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
    130                 135                 140

gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg  480
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145                 150                 155                 160

aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca tag      525
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
            165                 170
```

<210> 66
<211> 174
<212> PRT
<213> Homo sapiens

<400> 66
```
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 1               5                  10                  15
```

```
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
            20                  25                  30

Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
        35                  40                  45

Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
    50                  55                  60

Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
65                  70                  75                  80

Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                85                  90                  95

Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
        115                 120                 125

Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
    130                 135                 140

Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145                 150                 155                 160

Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
                165                 170
```

<210> 67
<211> 444
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(444)

<400> 67

```
atg gct ggt cgt cac gtt cgt tct tac aac cac ctg cag ggt gac gtt   48
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
  1               5                  10                  15

cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa atc gaa   96
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
            20                  25                  30

aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg tac agc   144
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
        35                  40                  45

atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc   192
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
    50                  55                  60

att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat   240
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
65                  70                  75                  80
```

```
ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg ata gag   288
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu
                 85                  90                  95

gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat aat ggg   336
Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly
            100                 105                 110

agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg aga gga   384
Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly
        115                 120                 125

cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg   432
Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val
    130                 135                 140

gta cac tca tag                                                  444
Val His Ser
145
```

<210> 68
<211> 147
<212> PRT
<213> Homo sapiens

<400> 68

```
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
  1               5                  10                  15
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
             20                  25                  30
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
         35                  40                  45
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
     50                  55                  60
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
 65                  70                  75                  80
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu
                 85                  90                  95
Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly
            100                 105                 110
Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly
        115                 120                 125
Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val
    130                 135                 140
Val His Ser
145
```

<210> 69
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(402)

<400> 69

```
atg gtt cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa   48
Met Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys
```

```
  1               5                  10                  15

atc gaa aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg   96
Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
            20                  25                  30

tac agc atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc   144
Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
        35                  40                  45

aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa   192
Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
    50                  55                  60

ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg   240
Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
65                  70                  75                  80

ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat   288
Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
                85                  90                  95

aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg   336
Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
            100                 105                 110

aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca   384
Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro
        115                 120                 125

atg gtg gta cac tca tag                                          402
Met Val Val His Ser
    130
```

<210> 70
<211> 133
<212> PRT
<213> Homo sapiens

<400> 70

```
Met Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys
  1               5                  10                  15
Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
            20                  25                  30
Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
        35                  40                  45
Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
    50                  55                  60
Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
65                  70                  75                  80
Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
                85                  90                  95
Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
            100                 105                 110
Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro
        115                 120                 125
Met Val Val His Ser
    130
```

<210> 71
<211> 354
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(354)

<400> 71
```
atg gaa aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg   48
Met Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
  1               5                  10                  15

tac agc atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc   96
Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
             20                  25                  30

aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa   144
Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
         35                  40                  45

ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg   192
Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
     50                  55                  60

ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat   240
Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
 65                  70                  75                  80

aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg   288
Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
                 85                  90                  95

aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca   336
Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro
            100                 105                 110

atg gtg gta cac tca tag                                          354
Met Val Val His Ser
        115
```

<210> 72
<211> 117
<212> PRT
<213> Homo sapiens

<400> 72
```
Met Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
  1               5                  10                  15
Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
             20                  25                  30
Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
         35                  40                  45
Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
     50                  55                  60
Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
 65                  70                  75                  80
Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
                 85                  90                  95
Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro
```

```
            100                 105                 110
Met Val Val His Ser
        115
```

<210> 73
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(321)

<400> 73

```
atg gag aac tgc ccg tac agc atc ctg gag ata aca tca gta gaa atc   48
Met Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile
  1               5                  10                  15

gga gtt gtt gcc gtc aaa gcc att aac agc aac tat tac tta gcc atg   96
Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met
             20                  25                  30

aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt   144
Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
         35                  40                  45

aag ctg aag gag agg ata gag gaa aat gga tac aat acc tat gca tca   192
Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser
     50                  55                  60

ttt aac tgg cag cat aat ggg agg caa atg tat gtg gca ttg aat gga   240
Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly
 65                  70                  75                  80

aaa gga gct cca agg aga gga cag aaa aca cga agg aaa aac acc tct   288
Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser
                 85                  90                  95

gct cac ttt ctt cca atg gtg gta cac tca tag                      321
Ala His Phe Leu Pro Met Val Val His Ser
            100                 105
```

<210> 74
<211> 106
<212> PRT
<213> Homo sapiens

<400> 74

```
Met Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile
  1               5                  10                  15
Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met
             20                  25                  30
Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
         35                  40                  45
Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser
     50                  55                  60
Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly
 65                  70                  75                  80
Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser
```

```
                85                  90                  95
Ala His Phe Leu Pro Met Val Val His Ser
            100                 105
```

<210> 75
<211> 264
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(261)

<400> 75

```
atg gtc aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag   48
Met Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys
  1               5                  10                  15

ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag   96
Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
             20                  25                  30

gag agg ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg   144
Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp
         35                  40                  45

cag cat aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct   192
Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala
     50                  55                  60

cca agg aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt   240
Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe
 65                  70                  75                  80

ctt cca atg gtg gta cac tca tag                                  264
Leu Pro Met Val Val His Ser
                85
```

<210> 76
<211> 87
<212> PRT
<213> Homo sapiens

<400> 76

```
Met Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys
  1               5                  10                  15

Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
             20                  25                  30

Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp
         35                  40                  45

Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala
     50                  55                  60

Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe
 65                  70                  75                  80
```

```
Leu Pro Met Val Val His Ser
                 85



<210> 77
<211> 219
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(219)

<400> 77
atg ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg   48
Met Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
  1               5                  10                  15

aag gag agg ata gag gaa aat gga tac aat acc tat gca tca ttt aac   96
Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
             20                  25                  30

tgg cag cat aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga   144
Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
         35                  40                  45

gct cca agg aga gga cag aaa aca cga agg aaa aac acc tct gct cac   192
Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
     50                  55                  60

ttt ctt cca atg gtg gta cac tca tag                              219
Phe Leu Pro Met Val Val His Ser
 65                  70


<210> 78
<211> 72
<212> PRT
<213> Homo sapiens

<400> 78
Met Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
  1               5                  10                  15
Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
             20                  25                  30
Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
         35                  40                  45
Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
     50                  55                  60
Phe Leu Pro Met Val Val His Ser
 65                  70



<210> 79
<211> 357
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
```

<222> (1)..(357)

<400> 79

```
atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc   48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1               5                  10                  15

aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac   96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20                  25                  30

gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg   144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt   192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca   240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat   288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt   336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110

aac aat gac tgt aag ctg aag                                      357
Asn Asn Asp Cys Lys Leu Lys
        115
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<210> 80
<211> 119
<212> PRT
<213> Homo sapiens

<400> 80

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Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1               5                  10                  15

Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20                  25                  30

Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
         35                  40                  45

Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
     50                  55                  60

Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65                  70                  75                  80

Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
                 85                  90                  95

Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
            100                 105                 110
```

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Asn Asn Asp Cys Lys Leu Lys
        115
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<210> 81
<211> 276
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(276)

<400> 81

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atg gct ggt cgt cac gtt cgt tct tac aac cac ctg cag ggt gac gtt   48
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
  1               5                  10                  15

cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa atc gaa   96
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
             20                  25                  30

aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg tac agc   144
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
         35                  40                  45

atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc   192
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
     50                  55                  60

att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat   240
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
 65                  70                  75                  80

ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag                   276
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
                85                  90
```

<210> 82
<211> 92
<212> PRT
<213> Homo sapiens

<400> 82

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Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
  1               5                  10                  15

Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
             20                  25                  30

Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
         35                  40                  45

Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
     50                  55                  60

Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
 65                  70                  75                  80

Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
```

85 90

<210> 83
<211> 525
<212> DNA
<213> Homo sapiens

<400> 83
atgacctctc aggctctggg tcaggacatg gtttctccgg aagctaccaa ctcttcctct 60
tcctctttct cttccccgtc ttccgctggt cgtcacgttc gttcttacaa ccacctgcag 120
ggtgacgttc gttggcgtaa actgttctct ttcaccaaat acttcctgaa aatcgaaaaa 180
aacggtaaag tttctgggac caagaaggag aactctccgt acagcatcct ggagataaca 240
tcagtagaaa tcggagttgt tgccgtcaaa gccattaaca gcaactatta cttagccatg 300
aacaagaagg ggaaactcta tggctcaaaa gaatttaaca atgactgtaa gctgaaggag 360
aggatagagg aaaatggata caatacctat gcatcattta actggcagca taatgggagg 420
caaatgtatg tggcattgaa tggaaaagga gctccaagga gaggacagaa aacacgaagg 480
aaaaacacct ctgctcactt tcttccaatg gtggtacact catag 525

<210> 84
<211> 525
<212> DNA
<213> Homo sapiens

<400> 84
atgacctgcc aggctctggg tcaggacatg gtttctccgg aagctaccaa ctcttcctct 60
tcctctttct cttccccgtc ttccgctggt cgtcacgttc gttcttacaa ccacctgcag 120
ggtgacgttc gttggcgtaa actgttctct ttcaccaaat acttcctgaa aatcgaaaaa 180
aacggtaaag tttctgggac caagaaggag aactctccgt acagcatcct ggagataaca 240
tcagtagaaa tcggagttgt tgccgtcaaa gccattaaca gcaactatta cttagccatg 300
aacaagaagg ggaaactcta tggctcaaaa gaatttaaca atgactgtaa gctgaaggag 360
aggatagagg aaaatggata caatacctat gcatcattta actggcagca taatgggagg 420
caaatgtatg tggcattgaa tggaaaagga gctccaagga gaggacagaa aacacgaagg 480
aaaaacacct ctgctcactt tcttccaatg gtggtacact catag 525

<210> 85
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 85
ggaccctcat gacctctcag gctctgggt 29

<210> 86
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 86
aaggagaact ctccgtacag c 21

<210> 87
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 87
gctgtacggt ctgttctcct t 21

<210> 88
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 88
ggaccctcat gacctgccag gctctgggtc aggac 35

<210> 89
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 89
ctgcccaagc ttattatgag tgtaccacca ttggaag 37

<210> 90
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 90
aaaggatcct gccaggctct gggtcaggac atg 33

<210> 91
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 91
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 92
<211> 28

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 92
gggcccaagc ttatgagtgt accaccat 28

<210> 93
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 93
ccggcggatc ccatatgtct tacaaccacc tgcagg 36

<210> 94
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 94
ccggcggtac cttattatga gtgtaccacc attgg 35

<210> 95
<211> 426
<212> DNA
<213> Homo sapiens

<400> 95
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacaga aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcataa 426

<210> 96
<211> 141
<212> PRT
<213> Homo sapiens

<400> 96
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

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Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
         35                  40                  45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
     50                  55                  60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65                  70                  75                  80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
                 85                  90                  95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
            100                 105                 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
        115                 120                 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
    130                 135                 140
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<210> 97
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 97
caaccacctg cagggtgacg 20

<210> 98
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 98
aacggtcgac aaatgtatgt ggcactgaac ggtaaaggtg ctccacgtcg tggtcagaaa 60
acccgtcgta aaaacacc 78

<210> 99
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 99
gggcccaagc ttaagagtgt accaccattg gcagaaagtg agcagaggtg tttttacgac 60
gggttttctg accacg 76

<210> 100
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 100
gccacataca tttgtcgacc gtt 23

<210> 101
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 101
gggcccaagc ttaagagtg 19

<210> 102
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 102
gccacataca tttgtcgacc gtt 23

<210> 103
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 103
ctgcagggtg acgttcgttg gcgtaaactg ttctccttca ccaaatactt cctgaaaatc 60
gaaaaaaacg gtaaagtttc tggtaccaag 90

<210> 104
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 104
agctttaaca gcaacaacac cgatttcaac ggaggtgatt tccaggatgg agtacgggca 60
gttttctttc ttggtaccag aaactttacc 90

<210> 105
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 105
ggtgttgttg ctgttaaagc tatcaactcc aactactacc tggctatgaa caagaaaggt 60
aaactgtacg gttccaaaga atttaacaac 90

<210> 106
<211> 100
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 106
gtcgaccgtt gtgctgccag ttgaaggaag cgtaggtgtt gtaaccgttt tcttcgatac 60
gttctttcag tttacagtcg ttgttaaatt ctttggaacc 100

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 107
gcggcgtcga ccgttgtgct gccag 25

<210> 108
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 108
gcggcctgca gggtgacgtt cgttgg 26

<210> 109
<211> 36
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 109
ccggcggatc ccatatgtct tacaaccacc tgcagg 36

<210> 110
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 110
cgcgcgatat cttattaaga gtgtaccacc attg 34

<210> 111
<211> 426
<212> DNA
<213> Homo sapiens

<400> 111
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc cttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggta ccaagaaaga aaactgcccg 120
tactccatcc tggaaatcac ctccgttgaa atcggtgttg ttgctgttaa agctatcaac 180
tccaactact acctggctat gaacaagaaa ggtaaactgt acggttccaa agaatttaac 240
aacgactgta aactgaaaga acgtatcgaa gaaaacggtt acaacaccta cgcttccttc 300
aactggcagc acaacggtcg acaaatgtat gtggcactga acggtaaagg tgctccacgt 360
cgtggtcaga aaacccgtcg taaaaacacc tctgctcact ttctgccaat ggtggtacac 420
tcttaa 426

<210> 112
<211> 141
<212> PRT
<213> Homo sapiens

<400> 112
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 113
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 113
cgcggccatg gctctgggtc aggacatg 28

<210> 114
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 114
gggcccaagc ttatgagtgt accaccat 28

<210> 115
<211> 516
<212> DNA
<213> Homo sapiens

<400> 115
atggctctgg gtcaagatat ggtttctccg gaagctacca actcttcctc ttcctctttc 60
tcttccccgt cttccgctgg tcgtcacgtt cgttcttaca accacctgca gggtgacgtt 120
cgttggcgta aactgttctc tttcaccaaa tacttcctga aaatcgaaaa aaacggtaaa 180
gtttctggga ccaagaagga gaactgcccg tacagcatcc tggagataac atcagtagaa 240
atcggagttg ttgccgtcaa agccattaac agcaactatt acttagccat gaacaagaag 300
gggaaactct atggctcaaa agaatttaac aatgactgta agctgaagga gaggatagag 360
gaaaatggat acaataccta tgcatcattt aactggcagc ataatgggag gcaaatgtat 420
gtggcattga atggaaaagg agctccaagg agaggacaga aaacacgaag gaaaaacacc 480
tctgctcact ttcttccaat ggtggtacac tcataa 516

<210> 116
<211> 171
<212> PRT
<213> Homo sapiens

<400> 116
Met Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser
1 5 10 15

```
Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser
            20                  25                  30

Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser Phe
        35                  40                  45

Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr
    50                  55                  60

Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu
65                  70                  75                  80

Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala
                85                  90                  95

Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp
            100                 105                 110

Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala
        115                 120                 125

Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn
    130                 135                 140

Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr
145                 150                 155                 160

Ser Ala His Phe Leu Pro Met Val Val His Ser
                165                 170
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<210> 117
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 117
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 118
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 118
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttttc 60
tcgtgttttc tgtcc 75

<210> 119
<211> 426
<212> DNA
<213> Homo sapiens

<400> 119

atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacaga aaacacgaga aaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 120
<211> 141
<212> PRT
<213> Homo sapiens

<400> 120
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Glu Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 121
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 121
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 122
<211> 75
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 122
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttctg 60
tcgtgttttc tgtcc 75

<210> 123
<211> 426
<212> DNA
<213> Homo sapiens

<400> 123
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacaga aaacacgaca gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 124
<211> 141
<212> PRT
<213> Homo sapiens

<400> 124
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Gln Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 125
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 125
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 126
<211> 84
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 126
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttcct 60
tcgtgtttcc tgtcctctcc ttgg 84

<210> 127
<211> 426
<212> DNA
<213> Homo sapiens

<400> 127
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacagg aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 128
<211> 141
<212> PRT
<213> Homo sapiens

<400> 128
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Glu Thr Arg Arg Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 129
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 129
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 130
<211> 84
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 130
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttcct 60
tcgtgtctgc tgtcctctcc ttgg 84

<210> 131
<211> 426
<212> DNA
<213> Homo sapiens

<400> 131
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacagc agacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 132
<211> 141
<212> PRT
<213> Homo sapiens

<400> 132
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Gln Thr Arg Arg Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 133
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 133
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 134
<211> 93
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 134
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttcct 60
tcgtgttttc tgtccttccc ttggagctcc ttt 93

<210> 135
<211> 426
<212> DNA
<213> Homo sapiens

<400> 135
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
gaaggacaga aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 136
<211> 140

<212> PRT
<213> Homo sapiens

<400> 136
Met Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser
1 5 10 15

Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly
20 25 30

Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val
35 40 45

Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu
50 55 60

Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn
65 70 75 80

Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr
85 90 95

Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu
100 105 110

Asn Gly Lys Gly Ala Pro Arg Glu Gly Gln Lys Thr Arg Arg Lys Asn
115 120 125

Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 137
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 137
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 138
<211> 93
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 138
ctgcccaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttcct 60
tcgtgttttc tgtccctgcc ttggagctcc ttt 93

<210> 139
<211> 426
<212> DNA
<213> Homo sapiens

<400> 139
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
cagggacaga aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 140
<211> 141
<212> PRT
<213> Homo sapiens

<400> 140
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Gln Gly Gln Lys Thr Arg Arg Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 141
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 141
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 142
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 142
ttgaatggag aaggagctcc a 21

<210> 143
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 143
tggagctcct tctccattca a 21

<210> 144
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 144
ctgcccaagc ttttatgagt gtaccaccat tgg 33

<210> 145
<211> 426
<212> DNA
<213> Homo sapiens

<400> 145
atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggagaagg agctccaagg 360
agaggacaga aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 146
<211> 141
<212> PRT
<213> Homo sapiens

<400> 146
Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

Leu Asn Gly Glu Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
130 135 140

<210> 147
<211> 3974
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: pHE4-5 vector

<400> 147
ggtacctaag tgagtagggc gtccgatcga cggacgcctt ttttttgaat tcgtaatcat 60
ggtcatagct gtttcctgtg tgaaattgtt atccgctcac aattccacac aacatacgag 120
ccggaagcat aaagtgtaaa gcctggggtg cctaatgagt gagctaactc acattaattg 180
cgttgcgctc actgcccgct ttccagtcgg gaaacctgtc gtgccagctg cattaatgaa 240
tcggccaacg cgcggggaga ggcggtttgc gtattgggcg ctcttccgct tcctcgctca 300
ctgactcgct gcgctcggtc gttcggctgc ggcgagcggt atcagctcac tcaaaggcgg 360
taatacggtt atccacagaa tcaggggata acgcaggaaa gaacatgtga gcaaaaggcc 420
agcaaaaggc caggaaccgt aaaaaggccg cgttgctggc gtttttccat aggctccgcc 480
cccctgacga gcatcacaaa aatcgacgct caagtcagag gtggcgaaac ccgacaggac 540
tataaagata ccaggcgttt ccccctggaa gctccctcgt gcgctctcct gttccgaccc 600
tgccgcttac cggatacctg tccgcctttc tcccttcggg aagcgtggcg ctttctcata 660
gctcacgctg taggtatctc agttcggtgt aggtcgttcg ctccaagctg ggctgtgtgc 720
acgaaccccc cgttcagccc gaccgctgcg ccttatccgg taactatcgt cttgagtcca 780
acccggtaag acacgactta tcgccactgg cagcagccac tggtaacagg attagcagag 840
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gaagaacagt atttggtatc tgcgctctgc tgaagccagt taccttcgga aaaagagttg 960
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agcagattac gcgcagaaaa aaaggatctc aagaagatcc tttgatcttt tctacggggt 1080
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acctttcgcg gtatggcatg atagcgcccg gaagagagtc aattcagggt ggtgaatgtg 1260
aaaccagtaa cgttatacga tgtcgcagag tatgccggtg tctcttatca gaccgtttcc 1320
cgcgtggtga accaggccag ccacgtttct gcgaaaacgc gggaaaaagt ggaagcggcg 1380
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gcgattaaat ctcgcgccga tcaactgggt gccagcgtgg tggtgtcgat ggtagaacga 1560
agcggcgtcg aagcctgtaa agcggcggtg cacaatcttc tcgcgcaacg cgtcagtggg 1620
ctgatcatta actatccgct ggatgaccag gatgccattg ctgtggaagc tgcctgcact 1680
aatgttccgg cgttatttct tgatgtctct gaccagacac ccatcaacag tattattttc 1740
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atcgcgctgt tagcgggccc attaagttct gtctcggcgc gtctgcgtct ggctggctgg 1860
cataaatatc tcactcgcaa tcaaattcag ccgatagcgg aacgggaagg cgactggagt 1920
gccatgtccg gttttcaaca aaccatgcaa atgctgaatg agggcatcgt tcccactgcg 1980
atgctggttg ccaacgatca gatggcgctg ggcgcaatgc gcgccattac cgagtccggg 2040

ctgcgcgttg gtgcggatat ctcggtagtg ggatacgacg ataccgaaga cagctcatgt 2100
tatatcccgc cgttaaccac catcaaacag gattttcgcc tgctggggca aaccagcgtg 2160
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tcactggtga aaagaaaaac caccctggcg cccaatacgc aaaccgcctc tccccgcgcg 2280
ttggccgatt cattaatgca gctggcacga caggtttccc gactggaaag cgggcagtga 2340
gcgcaacgca attaatgtaa gttagcgcga attgtcgacc aaagcggcca tcgtgcctcc 2400
ccactcctgc agttcggggg catggatgcg cggatagccg ctgctggttt cctggatgcc 2460
gacggatttg cactgccggt agaactccgc gaggtcgtcc agcctcaggc agcagctgaa 2520
ccaactcgcg aggggatcga gcccggggtg ggcgaagaac tccagcatga gatccccgcg 2580
ctggaggatc atccagccgg cgtcccggaa aacgattccg aagcccaacc tttcatagaa 2640
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gaaccccaga gtcccgctca gaagaactcg tcaagaaggc gatagaaggc gatgcgctgc 2760
gaatcgggag cggcgatacc gtaaagcacg aggaagcggt cagcccattc gccgccaagc 2820
tcttcagcaa tatcacgggt agccaacgct atgtcctgat agcggtccgc cacacccagc 2880
cggccacagt cgatgaatcc agaaaagcgg ccattttcca ccatgatatt cggcaagcag 2940
gcatcgccat gggtcacgac gagatcctcg ccgtcgggca tgcgcgcctt gagcctggcg 3000
aacagttcgg ctggcgcgag cccctgatgc tcttcgtcca gatcatcctg atcgacaaga 3060
ccggcttcca tccgagtacg tgctcgctcg atgcgatgtt tcgcttggtg gtcgaatggg 3120
caggtagccg gatcaagcgt atgcagccgc cgcattgcat cagccatgat ggatactttc 3180
tcggcaggag caaggtgaga tgacaggaga tcctgccccg gcacttcgcc caatagcagc 3240
cagtcccttc ccgcttcagt gacaacgtcg agcacagctg cgcaaggaac gcccgtcgtg 3300
gccagccacg atagccgcgc tgcctcgtcc tgcagttcat tcagggcacc ggacaggtcg 3360
gtcttgacaa aaagaaccgg gcgcccctgc gctgacagcc ggaacacggc ggcatcagag 3420
cagccgattg tctgttgtgc ccagtcatag ccgaatagcc tctccaccca agcggccgga 3480
gaacctgcgt gcaatccatc ttgttcaatc atgcgaaacg atcctcatcc tgtctcttga 3540
tcagatcttg atcccctgcg ccatcagatc cttggcggca agaaagccat ccagtttact 3600
ttgcagggct tcccaacctt accagagggc gccccagctg gcaattccgg ttcgcttgct 3660
gtccataaaa ccgcccagtc tagctatcgc catgtaagcc cactgcaagc tacctgcttt 3720
ctctttgcgc ttgcgttttc ccttgtccag atagcccagt agctgacatt catccggggt 3780
cagcaccgtt tctgcggact ggctttctac gtgttccgct tcctttagca gcccttgcgc 3840
cctgagtgct tgcggcagcg tgaagcttaa aaaactgcaa aaaatagttt gacttgtgag 3900
cggataacaa ttaagatgta cccaattgtg agcggataac aatttcacac attaaagagg 3960
agaaattaca tatg 3974

<210> 148
<211> 112
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: pHE4-5
promoter sequence

<400> 148
aagcttaaaa aactgcaaaa aatagtttga cttgtgagcg gataacaatt aagatgtacc 60
caattgtgag cggataacaa tttcacacat taaagaggag aaattacata tg 112

<210> 149
<211> 106
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 149
gagcgcggat ccgccaccat gaaggtctcc gtggctgccc tctcctgcct catgcttgtt 60
actgcccttg gatctcaggc cagctacaat caccttcaag gagatg 106

<210> 150
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 150
gagcgcggat ccctatgagt gtaccaccat tggaag 36

<210> 151
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 151
ccggccatat gcgtaaactg ttctctttca cc 32

<210> 152
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 152
ccggcggtac cttattatga gtgtaccacc attgg 35

<210> 153
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 153
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 154
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 154
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 155
<211> 32

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 155
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 156
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 156
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 157
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 157
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 158
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 158
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 159
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 159
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 160
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 160
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 161
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 161
gatcgcggat ccgccaccat gtggaaatgg atactgacac attgtgc 47

<210> 162
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 162
gatcgctcta gattatgagt gtaccaccat tggaagaaag 40

<210> 163
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 163
gatcgcggat ccgccaccat gtggaaatgg atactgacac attgtgc 47

<210> 164
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 164
gatcgctcta gattatgagt gtaccaccat tggaagaaag 40

<210> 165
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 165
gatcgcggat ccgccaccat gtggaaatgg atactgacac attgtgc 47

<210> 166
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 166
gatcgctcta gattatgagt gtaccaccat tggaagaaag 40

<210> 167
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 167
gatcgcggat ccgccaccat gtggaaatgg atactgacac attgtgc 47

<210> 168
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 168
gatcgctcta gattatgagt gtaccaccat tggaagaaag 40

<210> 169
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 169
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 170
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 170
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 171
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 171
gatcgccata tggctggtcg tcacgttcgt tc 32

<210> 172
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 172
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 173
<211> 456
<212> DNA
<213> Escherichia coli

<400> 173
catatggctg gtcgtcacgt tcgttcttac aaccacctgc agggtgacgt tcgttggcgt 60
aaactgttct ctttcaccaa atacttcctg aaaatcgaaa aaaacggtaa agtttctggg 120
accaagaagg agaactgccc gtacagcatc ctggagataa catcagtaga aatcggagtt 180
gttgccgtca aagccattaa cagcaactat tacttagcca tgaacaagaa ggggaaactc 240
tatggctcaa aagaatttaa caatgactgt aagctgaagg agaggataga ggaaaatgga 300
tacaatacct atgcatcatt taactggcag cataatggga ggcaaatgta tgtggcattg 360
aatggaaaag gagctccaag gagaggacag aaaacacgaa ggaaaaacac ctctgctcac 420
tttcttccaa tggtggtaca ctcataataa ggtacc 456

<210> 174
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 174
gactacatat ggctggtcgt cacgttcgtt cttacaacca cctgcagg 48

<210> 175
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 175

ctagtctcta gattattatg agtgtacaac catcggcagg aagtgag 47

<210> 176
<211> 447
<212> DNA
<213> Escherichia coli

<400> 176
atggctggtc gtcacgttcg ttcttacaac cacctgcagg gtgacgttcg ttggcgtaaa 60
ctgttctctt tcaccaaata cttcctgaaa atcgaaaaga acggtaaagt ttctggtacc 120
aagaaagaaa actgcccgta ctctatcctg gaaatcacct ccgttgaaat cggtgttgta 180
gccgttaaag ccatcaactc caactattac ctggccatga acaaaaaggg taaactgtac 240
ggctctaaag aattcaacaa cgactgcaaa ctgaaagaac gtatcgaaga gaacggttac 300
aacacctacg catccttcaa ctggcagcac aacggtcgtc agatgtacgt tgcactgaac 360
ggtaaaggcg ctccgcgtcg cggtcagaaa acccgtcgca aaaacacctc tgctcacttc 420
ctgccgatgg ttgtacactc ataataa 447